ALKOXYARYLOXYKETONES AND THEIR CONDENSATION WITH ISATINS

A THESIS

Presented to

the Faculty of the Division of Graduate Studies

Georgia School of Technology

In Partial Fulfillment

of the Requirements for the Degree

Master of Science in Chemistry

by

Robert Lewis Sublett

December 1947

ALKOXYARYLOXYKETONES AND THEIR

CONDENSATION WITH ISATINS

Approved:

_____

_____

_____

Date Approved by Chairman _____

ACKNOWLEDGMENTS

On the completion of this work I wish to express my sincere appreciation and gratitude to Dr. Paul K. Calaway, not only for suggesting the problem, but also for inspiration, aid, and guidance during its prosecution.

TABLE OF CONTENTS

CHAPTER I

PFITZINGER REACTION

ALKOXYARYLOXYKETONES AND THEIR CONDENSATION WITH ISATINS

CHAPTER I

THE PFITZINGER REACTION

The preparation of quinoline derivatives by the condensation of isatins with ketones may be attributed to Pfitzinger, who prepared 6-methyl-4-quinaldinecarboxylic acid by the condensation of 5-methylisatin with acetone.[1,2]

The Pfitzinger Reaction has been extended by Calaway and co-workers to include the condensation of aryloxyketones, arylthioketones, tolyloxyketones, and naphthoxyketones with isatins.[3,4,5,6]

The chief product of the condensation of unsymmetrical ketones with isatins will normally have the larger group in the 3-position.[7,8]

---

[1]Pfitzinger, J. prakt. Chem., 33, 100 (1886)

[2]Pfitzinger, J. prakt. Chem., 38, 584 (1888)

[3]Calaway and Henze, J. Am. Chem. Soc., 61, 1355 (1939)

[4]Knight, Porter, and Calaway, J. Am. Chem. Soc., 66, 1893 (1944)

[5]Newell and Calaway, J. Am. Chem. Soc., 69, 116 (1947)

[6]Dowell, McCullough, and Calaway, to be published

[7]Pfitzinger, J. prakt. Chem., 56, 283 (1897)

[8]Von Braun, Gmelin, and Schulthesis, Ber., 56, 1344 (1923)

CHAPTER II

PURPOSE OF THIS INVESTIGATION

CHAPTER II

PURPOSE OF THIS INVESTIGATION

The availability of alkoxyketones from chloroacetone and alkoxyphenols (courtesy of the Tennessee Eastman Company) suggested their condensation with isatin as a continuation of the work of Henze, Calaway,[3,4,5,6] and co-workers.

Experiments have shown that the quinoline group may exhibit marked pharmaceutical properties. Examples of substituted quinolines, whose effectiveness as anti-malarial drugs has been proven, are cinchopen, plasmochin, atoquinol, and quinine. Nupracaine is an example of a substituted quinoline which has anesthetic properties.

The substituted cinchoninic acids reported in this thesis are related in structure to these chemotherapeutic agents, and therefore may be of interest in the field of chemotherapy.

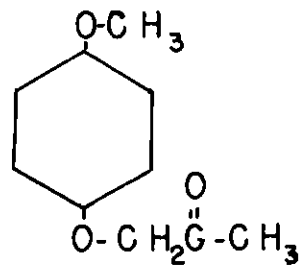
CHAPTER III

EXPERIMENTAL

CHAPTER III

EXPERIMENTAL

The Preparation of 1-(4-Methoxyphenoxy)-2-propanone (I)



(I)

1-(4-Methoxyphenoxy)-2-propanone (I) was prepared from chloroacetone and 4-methoxyphenol by the method of Hurd and Perlitz.[9]

Thirty grams (0.38 mole) of chloroacetone and 35 ml. of acetone (previously dried over calcium chloride) were mixed in a 125 ml. separatory funnel and three grams of potassium iodide was added. The mixture was shaken and allowed to stand overnight.

A solution of thirty-two grams (0.25 mole) of 4-methoxyphenol in 150 ml. of dry acetone was placed in a three-necked, one liter flask equipped with a mechanical stirrer, a reflux condenser, and a calcium chloride drying tube. The stirrer was started and thirty-eight grams (0.25 mole) of anhydrous potassium carbonate was added. After the reactants were refluxed over a hot water bath for fifteen minutes, the chloroacetone and potassium iodide were added slowly to the flask over

---

[9]Hurd and Perlitz, J. Am. Chem. Soc., 68, 38 (1946)

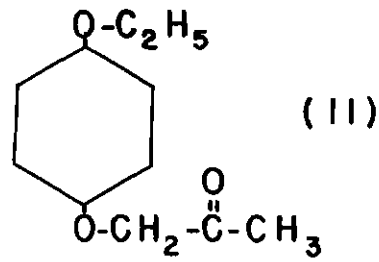
a period of one hour. The mixture was refluxed with stirring on a hot water bath for six hours and stirring continued at room temperature for twenty-four hours.

The reaction mixture was then filtered and the precipitate washed with acetone. The filtrate and washings were combined and concentrated by distillation at 35 mm. and 80 degrees. The concentrated filtrate was poured into a mixture of 400 ml. of ice and water. The crude product separated first as a heavy brown oil and upon stirring crystallized as a tan colored amorphous precipitate. The crude ketone was removed by filtration and air dried overnight. This crude product was purified initially by suspending it in 200 ml. of hot water, and adding methyl alcohol slowly until all the ketone was in solution. The hot solution was filtered and the filtrate cooled in ice until the ketone precipitated. The semi-crude product was separated by filtration and the above purification procedure repeated. Further purification was obtained by recrystallizing the ketone from cyclohexane.

The pure product was light tan in color and melted at 48.5 degrees C. (cor.). The yield was thirty grams, or 64% of theoretical. The 2, 4-dinitrophenylhydrazone was obtained as a yellow-orange crystalline solid melting at 149 degrees C. (cor.). The white semicarbazone melted at 192 degrees C. (cor.).

The preparation of this ketone was repeated and a yield of 80% of the theoretical was obtained by decreasing the time of stirring at room temperature from twenty-four to one hours.

Preparation of 1-(4-Ethoxyphenoxy)-2-propanone (II)



(II)

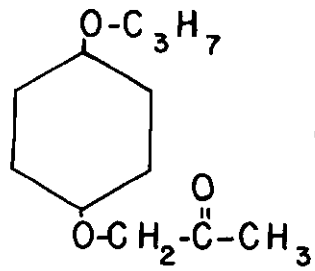
1-(4-Ethoxyphenoxy)-2-propanone (II) was prepared by the method of Hurd and Perlitz.[9]

Thirty grams (0.32 mole) of chloroacetone, three grams of powdered potassium iodide, and 50 ml. of dry acetone were mixed in a 125 ml. separatory funnel and allowed to stand overnight. The resulting solution was added slowly to a mixture of thirty grams (0.21 mole) of 4-ethoxyphenol, thirty-two grams (0.21 mole) of anhydrous potassium carbonate, and 150 ml. of dry acetone in a three-necked, one liter flask equipped with a mechanical stirrer and a reflux condenser. The procedure from this point was the same as in the preparation of 1-(4-methoxyphenoxy)-2-propanone (I). After the reaction was completed the potassium chloride was filtered off and washed with hot acetone. The filtrate and the washings were combined and concentrated at a pressure of approximately 35 mm. at 80 degrees C.

The ketone was precipitated and purified in the same manner as the 1-(4-methoxyphenoxy)-2-propanone (I). Due to the low melting point of 1-(4-ethoxyphenoxy)-2-propanone (II) an ice-salt bath was used. 1-(4-Ethoxyphenoxy)-2-propanone (II) melted at 35.5 degrees C. The yield was

26 grams (62% of theoretical). The 2,4-dinitrophenylhydrazone of this ketone was a light orange solid melting at 105.5 degrees C.(cor.). The semicarbazone was a white solid melting at 192 degrees C. (cor.).

Preparation of 1-(4-Propoxyphenoxy)-2-propanone (III)



(III)

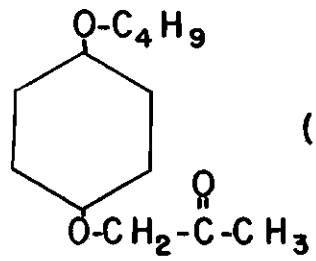
Thirty-five grams (0.38 mole) of chloroacetone, three grams of powdered potassium iodide, and 35 ml. of acetone were mixed in a 125 ml. separatory funnel and allowed to stand overnight. The mixture was then added to a solution of thirty-eight grams (0.25 mole) of 4-propoxyphenol in 150 ml. of acetone and thirty-eight grams (0.25 mole) of anhydrous potassium carbonate. The reaction was carried out in the same manner as in the preparation of 1-(4-methoxyphenoxy)-2-propanone (I). The inorganic salts were removed by filtration through a sintered glass funnel and washed with hot acetone. The filtrate and washings were combined and concentrated at a pressure of 35 mm. and a temperature of 80 degrees C.

The ketone was precipitated and purified in the same manner as the methoxy analog (I).

1-(4-Propoxyphenoxy)-2-propanone (III) was obtained in 73% yield as a light tan (almost white) solid melting at 39 degrees C. The 2,4-dinitrophenylhydrazone was a yellow-orange crystalline solid melting at 91.5 degrees C. (cor.). The semicarbazone melted at 189 degrees C. (cor.).

Upon repetition of the synthesis, decreasing the reaction time to three hours, the yield of 1-(4-propoxyphenoxy)-2-propanone (III) was increased to 85 %.

Preparation of 1-(4-Butoxyphenoxy)-2-propanone (IV)

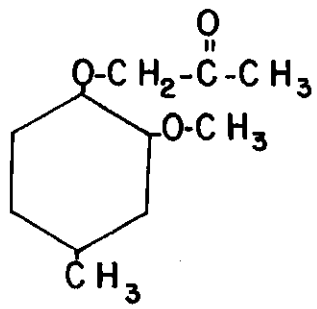


(IV)

1-(4-Butoxyphenoxy)-2-propanone (IV) was prepared by the interaction of 4-butoxyphenol and chloroacetone, and in exact accordance with the procedure of Hurd and Perlitz.[9] The ketone was obtained in 69% yield as a very light tan (almost white) solid which melted at 37 degrees C. (cor.).

The semicarbazone was prepared and melted at 188 degrees C. (cor.). The 2,4-dinitrophenylhydrazone was obtained as a yellow-orange crystalline solid, melting at 153 degrees C. (cor.).

Preparation of 1-(2-Methoxy-4-methyl)-2-propanone (V)



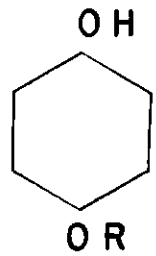
(V)

Thirty grams of chloroacetone, three grams of powdered potassium iodide and 50 ml. of acetone, mixed twenty-four hours previously, were added slowly to a one liter, three-necked flask containing thirty-three grams (0.22 mole) of anhydrous potassium carbonate and a hot solution of thirty grams (0.22 mole) of 2-methoxy-4-methyl phenol in 150 ml. of dry acetone. The reacting mixture was heated under reflux with stirring for six hours, and stirring was continued for twenty-four hours at room temperature.

The potassium carbonate and potassium chloride were removed by filtration and washed with hot acetone. The filtrate and washings were combined and concentrated. The precipitation and purification of the ketone were carried out in the same manner as for 1-(4-methoxyphenoxy)-2-propanone (I). A much lower melting point than exhibited by the previous ketones made crystallization more difficult and it was necessary to cool the cyclohexane solution in a dry ice-chloroform bath in order to cause precipitation of the product. The 1-(2-methoxy-4-methyl)-2-propanone (V) was obtained in 47% yield. The melting point was 28.5 degrees C. (cor.).

The dark yellow 2,4-dinitrophenylhydrazone melted at 136 degrees C. (cor.). The melting point of the semicarbazone was 153 degrees C. (cor.).

Preparation of Alkoxyphenols



(VI)

Most of the alkoxyphenols used in the preparation of the preceding ketones were furnished through the courtesy of the Tennessee Eastman Company. The 4-propoxyphenol was prepared in this laboratory by a method suggested by Dr. E. M. Reid.

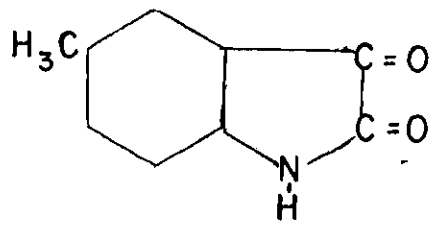
Two different methods were used. In the first fifty-five grams (0.5 mole) of hydroquinone and sixty-one grams (0.5 mole) of propylbromide were dissolved in 250 ml. of ethyl alcohol in a one liter round bottom flask equipped with two condensers in series. The mixture was boiled vigorously for ten minutes, and twenty grams (0.5 mole) of sodium hydroxide (50% solution) was slowly added through the top of the condenser. After thirty minutes of additional boiling, the flame was removed, thirty-three grams (0.55 mole) of acetic acid added, the reactant mixture concentrated under reduced pressure to one third the volume, and poured into 800 ml. of ice and water. The solid mass was removed by filtration.

The crude mixture, consisting of hydroquinone, 4-propoxyphenol, and 1,4-dipropoxybenzene, was transferred to a beaker containing 500 ml. of water, warmed to about 40 degrees for several minutes, and then filtered. This procedure was repeated several times until all the hydroquinone was removed. To the remaining 4-propoxyphenol and 1,4-dipropoxybenzene was

added 200 ml. of 10% sodium hydroxide solution. The mixture was warmed to 40 degrees and filtered while warm. The residue was treated again in the same manner. The filtrates were combined, acidified with hydrochloric acid, cooled in an ice bath, and filtered. The sodium hydroxide treatment was repeated without warming the solution. The pure product was air dried. The yield was twenty grams (26% of the theoretical). The melting point of the 4-propoxyphenol was 56 degrees C. (cor.).

In the second method one hundred ten grams (1.0 mole) of hydroquinone was dissolved in 500 ml. of ethyl alcohol in a round bottom flask equipped with two condensers, one above the other. The solution was boiled for several minutes to remove the air. Forty grams (1.0 mole) of sodium hydroxide (50% solution) was added through the top of the condenser. To the boiling solution was added, again through the condenser, one hundred twenty-three grams (1.0 mole) of propylbromide. Boiling was continued for one hour, and the hot solution acidified with hydrochloric acid (1-1). The crude product was purified in the same manner as outlined in the first method. The yield was fifty-nine grams (38% of theoretical). The melting point was 56 degrees C. (cor.).

Preparation of 5-Methylisatin (VII)[10]



(VII)

Ninety grams (0.54 mole) of chloral hydrate was dissolved in 1200 ml. of water in a five liter round bottom flask, and 1300 grams of crystalline sodium sulfate was added. A solution of fifty-four grams (0.5 mole) of p-toluidine in 300 ml. of water and 43 ml. (0.52 mole) of concentrated hydrochloric acid was added to the chloral hydrate solution, and this was followed by 110 grams (1.58 mole) of hydroxylamine hydrochloride in 500 ml. of water. The flask was then heated at such a rate as to produce boiling in forty-five to fifty minutes. The liquid was allowed to boil vigorously for two minutes, cooled rapidly, filtered, and the p-methylisonitrosoacetanilide air dried for twenty-four hours.

Six hundred grams (328 ml.) of concentrated sulfuric acid was warmed to 50 degrees in a one liter three-necked flask fitted with a mechanical stirrer and a thermometer, and the p-methylisonitrosoacetanilide was added with stirring at such a rate as to keep the temperature between 50 and 60 degrees C. After the addition of the isonitroso compound was complete, the solution was heated to 80 degrees for a period of ten minutes, cooled

---

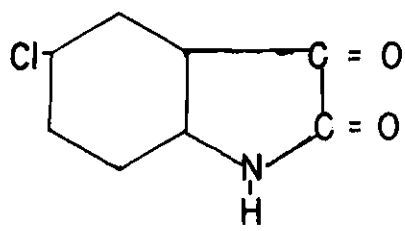
[10]Gilman, Organic Synthesis, Col. Vol. I, p. 321

under running water, poured over five liters of cracked ice, and allowed to stand until the ice melted.

The crude 5-methylisatin (VII) which separated out was filtered and washed free of sulfuric acid with cold water. The yield of the crude product was seventy-five grams (83% of the theoretical).

The crude 5-methylisatin (VII) was suspended in 400 ml. of hot water and 30% sodium hydroxide was added until the solid was in solution. Dilute hydrochloric acid (1 + 2) was added until a slight precipitate appeared. The hot solution was filtered immediately and the residue rejected. The filtrate was made acid to congo red paper with dilute hydrochloric acid, and the resulting solution cooled in an ice bath. The 5-methylisatin (VII) was filtered off and air dried. The resulting yield was approximately 80% of the crude product.

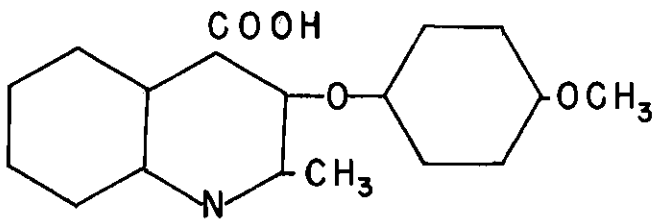
Preparation of 5-Chloroisatin (VIII)



(VIII)

5-Chloroisatin (VIII) was prepared by the exact procedure outlined for 5-methylisatin (VII), using p-chloroaniline in the place of p-toluidine. The purified final product, obtained in 75% yield, was a yellow solid melting at 246 degrees C. (cor.).

Preparation of 3-(4-Methoxyphenoxy)-4-quinaldinecarboxylic Acid (IX)



(IX)

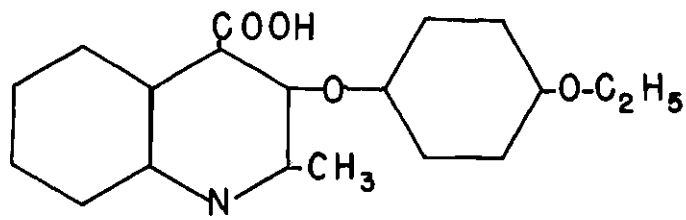
Fourteen and seven tenths grams (0.1 mole) of isatin was dissolved in 200 ml. of 33% aqueous potassium hydroxide and placed in a flask equipped with a mechanical stirrer. After the isatin was completely dissolved, seventeen grams (0.1 mole) of 1-(4-methoxyphenoxy)-2-propanone (I) was added. The mixture was heated with stirring over a water bath for six hours. Near the end of the reaction time a dark colored liquid had separated on the top of the aqueous layer. After standing for twenty-four hours, this liquid had solidified. The aqueous layer was decanted, acidified with acetic acid (1-1), and allowed to stand for several hours. Since no precipitate formed, the liquid was discarded.

The dark colored solid cake, consisting of crude potassium 3-(4-methoxyphenoxy)-4-quinaldinecarboxylate, that had been salted out of the original solution by the high concentration of potassium hydroxide, was broken up and dissolved in 400 ml. of boiling water. The boiling solution was treated with nuchar and filtered. The filtrate was a dark chocolate brown color. After cooling to room temperature, the filtrate was made acid to litmus paper with acetic acid (1-1). To secure complete precipitation of the quinoline acid the mixture was allowed to stand overnight and then filtered again. The crude product was suspended in 800 ml.

of hot water and enough 33% potassium hydroxide was added to convert the acid to the soluble potassium salt. The treatment with nuchar was repeated and after cooling, the filtrate once more acidified with acetic acid (1-1). The mixture was allowed to stand for several hours, the 3-(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (IX) filtered off, suspended in one liter of boiling water, and boiled for thirty minutes to remove the acetic acid. The quinoline acid was only slightly soluble in water as indicated by the fact that only one or two grams dissolved in the liter of boiling water. The product was dried over phosphorus pentoxide in a vacuum desiccator.

The 3-(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (IX) was a very light tan powder melting with decomposition at 215 degrees (cor.). This decomposition point varied with the rate of heating. The yield was twenty-three grams (74% of the theoretical). A small sample of the product was recrystallized from a large quantity of water and dried for several weeks over phosphorus pentoxide. This sample was used for the nitrogen analysis. The per cent nitrogen found experimentally was 4.20%; as compared with the calculated value of 4.56%.

Preparation of 3-(4-Ethoxyphenoxy)-4-quinaldinecarboxylic Acid (X)



(X)

The essential procedure for the preparation of 3-(4-ethoxyphenoxy)-4-quinaldinecarboxylic acid (X) was the same as for 3-(4-methoxyphenoxy-4-quinaldinecarboxylic acid (IX).

Fourteen and seven tenths grams (0.1 mole) of isatin was dissolved in 200 ml. of 33% aqueous potassium hydroxide in a flask equipped with a mechanical stirrer. When the isatin was completely dissolved, nineteen and four tenths grams (0.1 mole) of 1-(4-ethoxyphenoxy)-2-propanone (II) was added. The resulting mixture was heated, with constant stirring, on a steam bath for six hours; and after standing overnight at room temperature, a dark colored cake separated from the liquid. The aqueous layer was decanted off, diluted to five volumes, and acidified with acetic acid (1-1). Since no precipitate formed, the liquid was discarded.

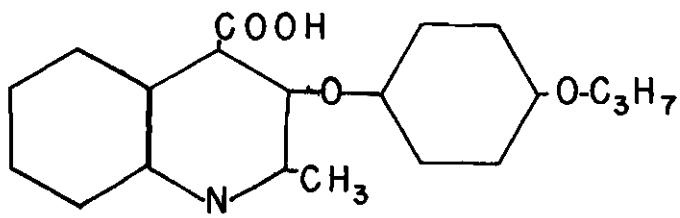
The solid cake was disintegrated and dissolved in 800 ml. of hot water. The resulting mixture was boiled for fifteen minutes with activated charcoal (nuchar), filtered, cooled to room temperature, and the quinoline acid precipitated with acetic acid (1-1). The solid was filtered off, suspended in 600 ml. of hot water, and converted to the soluble potassium salt by the addition of a small amount of 33% potassium hydroxide.

The nuchar treatment was repeated, and the quinoline acid suspended

in 600 ml. of hot water, boiled for ten minutes, cooled, and filtered. The hot water treatment was repeated and the pure product dried over phosphorus pentoxide. The yield was eighteen grams (56% of the theoretical).

A small sample of the product was recrystallized from a large quantity of water and used for a nitrogen analysis. The nitrogen determination gave a value of 4.19% as compared with the theoretical value of 4.33%. The compound darkened at about 150 degrees C. and melted at 214 degrees C. (cor.) with decomposition.

Preparation of 3-(4-Propoxyphenoxy)-4-quinaldinecarboxylic Acid (XI)



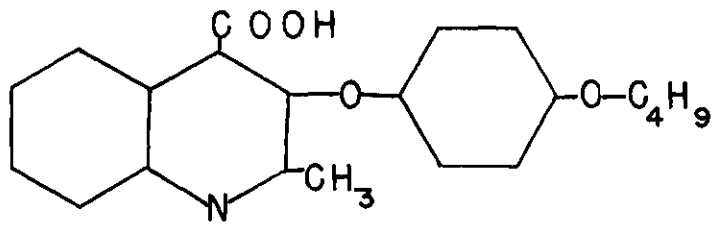
(XI)

Seven and four tenths grams (0.05 mole) of isatin was dissolved in 100 ml. of 33% aqueous potassium hydroxide. To this solution was added twenty-one grams (0.05 mole) of 1-(4-propoxyphenoxy)-2-propanone (III), and the resulting mixture stirred over a steam bath for three hours. Upon cooling overnight the potassium salt of 3-(4-propoxyphenoxy)-4-quinaldinecarboxylic acid (XI) separated out in the form of a soap-like cake. The liquid was decanted and acidified with a (1-1) solution of acetic acid, but no 3-(4-propoxyphenoxy)-4-quinaldinecarboxylic acid (XI) was obtained by this procedure.

The solid cake was dissolved in 800 ml. of hot water and purified in the usual manner. The purified product was light tan in color, melting with decomposition at 208 degrees C. (cor.). The yield was eleven grams (70% of the theoretical).

The per cent nitrogen found was 4.14%. The calculated value was 4.15%.

Preparation of 3-(4-Butoxyphenoxy)-4-quinaldinecarboxylic Acid (XII)



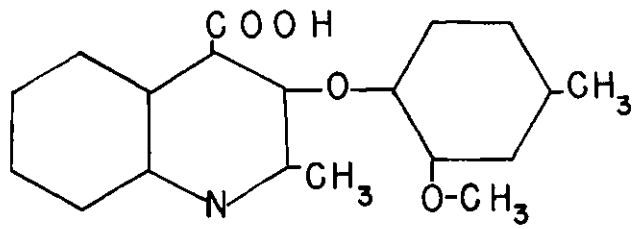
(XII)

In a flask equipped with a mechanical stirrer was placed a solution of fourteen and seven tenths grams (0.1 mole) of isatin dissolved in 200 ml. of 33% aqueous potassium hydroxide. Twenty-two and two tenths grams (0.1 mole) of 1-(4-butoxyphenoxy)-2-propanone (IV) was added and the mixture stirred over a steam bath for six hours. It was then cooled overnight and the potassium salt of 3-(4-butoxyphenoxy)-4-quinaldinecarboxylic acid (XII) separated out as a dark colored cake. The liquid portion was decanted, acidified with acetic acid (1-1), and then discarded because it contained no quinoline acid.

The potassium salt of 3-(4-butoxyphenoxy)-4-quinaldinecarboxylic acid (XII) was dissolved in 800 ml. of hot water and purified in the same manner as the preceding quinoline acids. The pure product was obtained in 77% yield as a light tan solid with a greenish cast, melting with decomposition at 150 degrees (cor.).

The small sample used for the nitrogen analysis was obtained by recrystallization from a large volume of water and dried over phosphorus pentoxide for several weeks. The per cent nitrogen found was 3.70%. The calculated value was 3.99%.

Preparation of 3-(2-Methoxy-4-methylphenoxy)-4-quinaldinecarboxylic Acid (XIII)



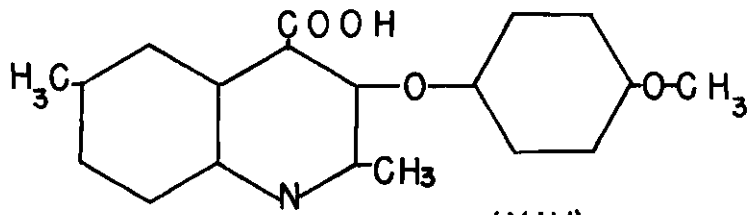
(XIII)

Nine and seven tenths grams (0.05 mole) of 1-(2-methoxy-4-methylphenoxy)-2-propanone (V) was added to a flask containing a solution of seven and four tenths grams (0.05 mole) of isatin in 100 ml. of 33% aqueous potassium hydroxide. The reaction mixture was heated on a steam bath with constant stirring for six hours; it was then cooled and allowed to stand overnight, but no solid cake separated.

The resulting liquid was diluted with cold water to 800 ml. and acidified with a (1-1) solution of acetic acid. The substituted quinoline acid precipitated as a finely divided dark brown solid. The crude product was purified in the usual manner. The air dried, purified product, a shade darker in color than the preceding quinoline acids, was obtained in 77% yield. The melting point was 232 degrees C. (cor.).

The per cent nitrogen found was 4.14%; the calculated value was 4.33%.

Preparation of 6-Methyl-3-(4-methoxyphenoxy)-4-quinaldinecarboxylic Acid (XIV)



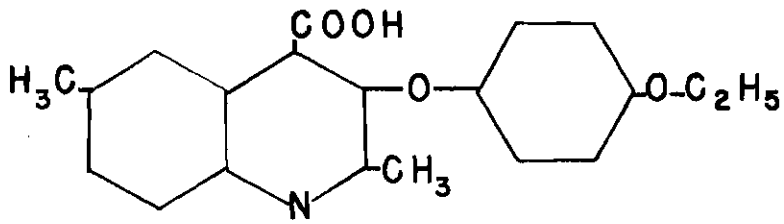
(XIV)

Eight grams (0.05 mole) of 5-methylisatin (VII) was dissolved in 100 ml. of 33% aqueous potassium hydroxide and placed in a flask equipped with a mechanical stirrer. To this solution was added eight and five tenths grams (0.05 mole) of 1-(4-methoxyphenoxy)-2-propanone (I). The mixture was heated on a steam bath with stirring for four hours and allowed to stand overnight at room temperature. At the end of this time a dark solid cake had formed. The liquid portion was decanted and acidified with (1-1) acetic acid. No precipitate formed and the liquid was discarded.

The solid cake was dissolved in 400 ml. of water, and the same purification method was used as for the preceding quinoline acids. The 6-methyl-3-(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (XIV) was obtained in 67% yield as a light tan powder melting with decomposition at 234 degrees C. (cor.).

The small sample used for nitrogen analysis was recrystallized from a large volume of water and dried over phosphorus pentoxide in a vacuum desiccator. The nitrogen analysis gave a nitrogen content of 4.25% as compared to the calculated value of 4.33%.

Preparation of 6-Methyl-3-(4-ethoxyphenoxy)-4-quinaldinecarboxylic Acid (XV)



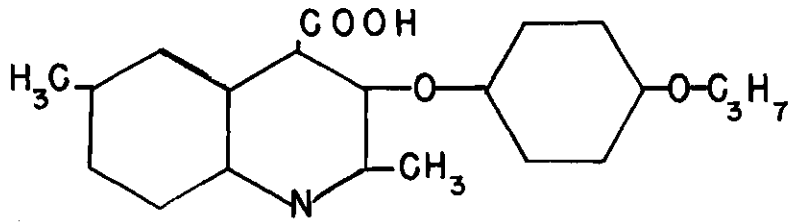
(XV)

Eight grams (0.05 mole) of 5-methylisatin (VII) was dissolved in 100 ml. of 33% aqueous potassium hydroxide solution and nine and seven tenths grams (0.05 mole) of 1-(4-ethoxyphenoxy)-2-propanone (II) was added. The resulting mixture was heated on a steam bath with stirring for five hours. After standing overnight at room temperature, a solid cake of potassium 6-methyl-3-(4-ethoxyphenoxy)-4-quinaldinecarboxylate separated in the reaction flask. The liquid portion was rejected.

The solid cake was dissolved in 400 ml. of water and the standard procedure for purification was followed. The 6-methyl-3-(4-ethoxyphenoxy)-4-quinaldinecarboxylic acid (XV) was a light tan powder, melting with decomposition at 198 degrees C. (cor.). The yield was twelve grams (71% of the theoretical).

A small sample was recrystallized from water and dried over phosphorus pentoxide in a vacuum desiccator. Analysis for nitrogen content gave a value of 4.30%, as compared with a calculated value of 4.15%.

Preparation of 6-Methyl-3-(4-propoxyphenoxy)-4-quinaldinecarboxylic Acid (XVI)



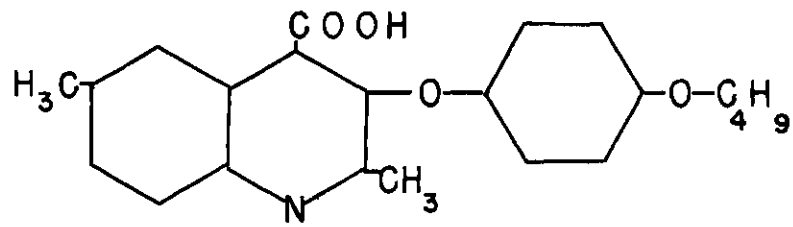
(XVI)

Ten and four tenths grams (0.05 mole) of 1-(4-propoxyphenoxy)-2-propanone (III) was added to a flask containing a solution of eight grams (0.05 mole) of 5-methylisatin (VII) in 100 ml. of 33% aqueous potassium hydroxide. The resulting mixture was heated on a steam bath with constant stirring for three hours. After cooling, the potassium 6-methyl-3-(4-propoxyphenoxy)-4-quinaldinecarboxylate separated from the liquid as a solid cake.

The liquid portion was rejected, and the solid cake was dissolved in 400 ml. of water and purified in the usual manner. The yield of the semi-crude product was eleven and five tenths grams (64% of the theoretical). The melting point, with decomposition, was 204 degrees C. (cor.).

A sample recrystallized from water was analyzed for nitrogen, and the value obtained (4.01%) checked the calculated percentage closely (3.99%).

Preparation of 6-Methyl-3-(4-butoxyphenoxy)-4-quinaldinecarboxylic Acid (XVII)



(XVII)

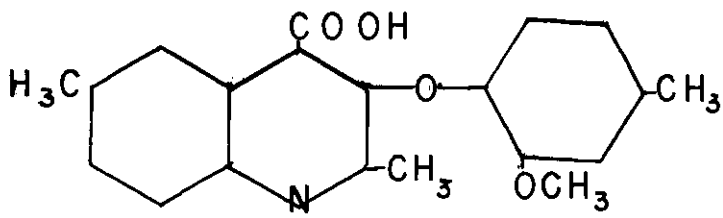
Eight grams (0.05 mole) of 5-methylisatin (VII) was dissolved in 100 ml. of 33% aqueous potassium hydroxide. Eleven and one tenth grams (0.05 mole) of 1-(4-butoxyphenoxy)-2-propanone (IV) was added to this solution and the mixture was heated over a steam bath for three hours with constant stirring.

After standing at room temperature for several hours, the potassium salt of 6-methyl-3-(4-butoxyphenoxy)-4-quinaldinecarboxylic acid (XVII) separated as a solid cake. This cake was broken up and dissolved in 400 ml. of water. The crude product was purified by the same method outlined for 3-(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (IX).

The pure product was a darker tan powder than the corresponding condensation product from isatin. 6-Methyl-3-(4-butoxyphenoxy)-4-quinaldinecarboxylic acid (XVII) melted with decomposition at 193 degrees C. (cor.). The yield was ten and five tenths grams (60% of the theoretical).

A nitrogen analysis was run on a small sample which had been recrystallized from a large volume of water and dried over phosphorus pentoxide in a vacuum desiccator. The value obtained (3.85%) checked the calculated value (3.83%).

Preparation of 6-Methyl-3-(2-methoxy-4-methylphenoxy)-4-quinaldinecarboxylic Acid (XVIII)



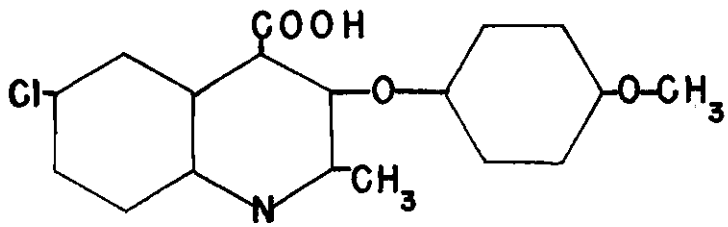
(XVIII)

Eight grams (0.05 mole) of 5-methylisatin (VII) was dissolved in 100 ml. of 33% aqueous potassium hydroxide and placed in a flask equipped with a mechanical stirrer. Nine and seven tenths grams (0.05 mole) of 1-(2-methoxy-4-methylphenoxy)-2-propanone (V) was added and the resulting mixture was heated with stirring on a steam bath for four hours and allowed to stand overnight at room temperature. No solid precipitated. The liquid was diluted to 400 ml. and acidified with (1-1) acetic acid.

The solid acid was removed by filtration and purified by the usual method. The purified 6-methyl-3-(2-methoxy-4-methylphenoxy)-4-quinaldinecarboxylic acid (XVIII) was obtained in 54% yield as a tan solid melting with decomposition at 242 degrees C. (cor.).

The nitrogen analysis gave a value of 4.19%. The calculated percentage is 4.15%.

Preparation of 6-Chloro-3-(4-methoxyphenoxy)-4-quinaldinecarboxylic Acid (XIX)



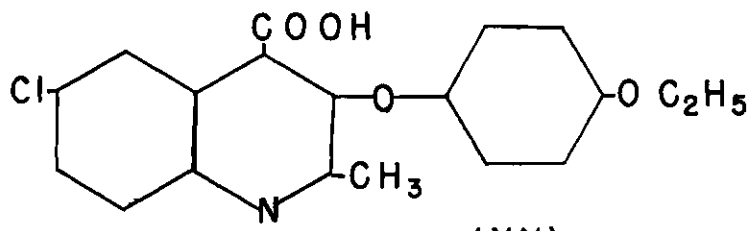
(XIX)

Nine and seven hundredths grams (0.05 mole) of 5-chloroisatin (VIII) was dissolved in 180 ml. of 33% aqueous potassium hydroxide, and eight and five tenths grams (0.05 mole) of 1-(4-methoxyphenoxy)-2-propanone (I) was added. The resulting mixture was heated with stirring on a steam bath for one hour. Upon cooling the potassium 6-chloro-3-(4-methoxyphenoxy)-4-quinaldinecarboxylate separated in the flask. The decanted liquid portion yielded no precipitate upon acidification with dilute acetic acid (1-1).

The solid material was dissolved in 400 ml. of water, boiled with nuchar, filtered, and cooled. The quinoline acid was precipitated with acetic acid (1-1). The product was separated by filtration, suspended in 400 ml. of hot water, and enough potassium hydroxide was added to dissolve the material. The nuchar treatment was repeated. The final product was a light tan (almost white solid, melting with decomposition at 237 degrees C. (cor.). The yield was seven grams (40% of the theoretical).

Analysis of a small sample previously dried over phosphorus pentoxide in a vacuum desiccator gave a value for nitrogen content of 4.00%. The calculated value is 4.08% nitrogen.

Preparation of 6-Chloro-3-(4-ethoxyphenoxy)-4-quinaldinecarboxylic Acid (XX)



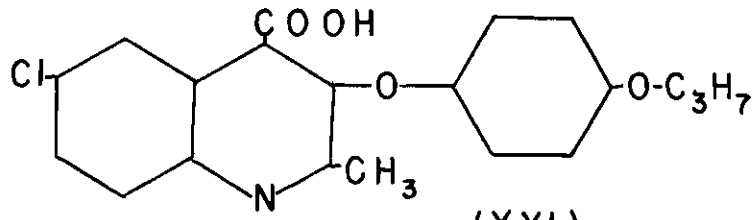
(XX)

In 200 ml. of 33% aqueous potassium hydroxide was dissolved nine and seven hundredths grams (0.05 mole) of 5-chloroisatin. To this solution was added nine and seven tenths (0.05 mole) of 1-(4-ethoxyphenoxy)-2-propanone (II). The mixture was heated with stirring on a steam bath for one hour, then cooled. The potassium salt of the quinoline acid separated in the flask. The solid and the liquid were separated. The liquid was discarded, and the solid was purified by the same method outlined for 6-chloro-3-(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (XIX).

The purified product was light tan in color and melted with decomposition at 222 degrees C. (cor.). The yield was fourteen and seven tenths grams (82% of the theoretical).

A small sample was dried over phosphorus pentoxide in a vacuum desiccator and analyzed for nitrogen. The experimental value of 3.66% was slightly lower than the calculated value of 3.91%.

Preparation of 6-Chloro-3-(4-propoxyphenoxy)-4-quinaldinecarboxylic Acid (XXI)



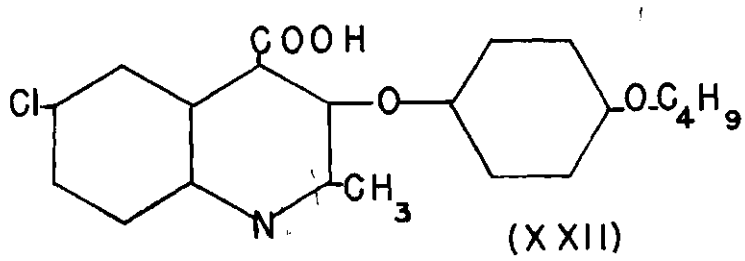
(XXI)

In 200 ml. of 33% aqueous potassium hydroxide was dissolved nine and seven hundredths grams (0.05 mole) of 5-chloroisatin (VIII). To this solution was added ten and four tenths grams (0.05 mole) of 1-(4-propoxyphenoxy)-2-propanone (III). The resulting mixture was heated with constant stirring on a steam bath for thirty minutes. After cooling, the potassium salt separated from the liquid, and it was subjected to the usual purification procedure.

The final product was light beige color, melting with decomposition at 205 degrees C. (cor.). The yield was twelve and five tenths grams (68% of the theoretical).

A quantitative nitrogen determination gave a value of 3.48%, as compared with the calculated value of 3.77%.

Preparation of 6-Chloro-3-(4-butoxyphenoxy)-4-quinaldinecarboxylic Acid (XXII)



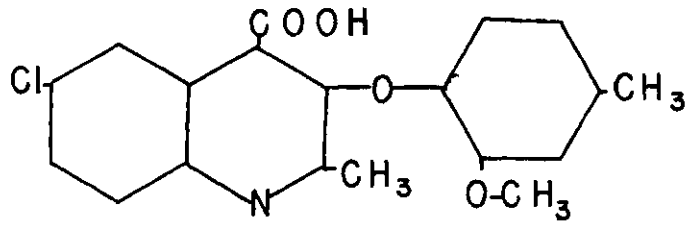
(XXII)

Nine and seven hundredths grams (0.05 mole) of 5-chloroisatin (VIII) was dissolved in 200 ml. of 33% aqueous potassium hydroxide. To this solution was added eleven and one tenth grams (0.05 mole) of 1-(4-butoxyphenoxy)-2-propanone (IV), and the reaction mixture was heated for thirty minutes on a steam bath. The reaction product was separated and purified in the usual manner.

The final product had a light tan cast and melted with decomposition at 163 degrees C. (cor.). The yield was twelve and nine tenths grams (67% of the theoretical).

The nitrogen content found by analysis of a small sample, dried over phosphorus pentoxide in a vacuum desiccator, was 3.70%. The calculated value was 3.63%.

Preparation of 6-Chloro-3-(2-methoxy-4-methylphenoxy)-4-quinaldinecarboxylic Acid (XXIII)



(XXIII)

Nine and seven tenths grams (0.05 mole) of 1-(2-methoxy-4-methylphenoxy)-2-propanone (V) was added to a solution of nine and seven hundredths grams (0.05 mole) of 5-chloroisatin (VIII) in 200 ml. of 33% aqueous potassium hydroxide. The mixture was refluxed on a steam bath for thirty minutes. The potassium 6-chloro-3-(2-methoxy-4-methylphenoxy)-4-quinaldinecarboxylate did not separate on cooling. The reaction liquid was diluted to 500 ml. and acidified with acetic acid (1-1). The precipitate was removed by filtration and purified by the same general procedure as for the preceding quinoline acids.

The final compound was brown in color, and melted with decomposition at 215 degrees C. (cor.). The yield was seven and five tenths grams (42% of the theoretical).

A quantitative nitrogen analysis gave a result of 3.73%. The theoretical value is 3.91%.

CHAPTER IV

GENERAL DISCUSSION OF RESULTS

GENERAL DISCUSSION OF RESULTS

The preparation of aryloxyketones by the Hurd and Perletz[9] Method has been extended to include several alkoxyaryloxyketones. These ketones were white solids melting slightly above room temperature. Upon standing they darkened to a light tan color.

The highest yield (82%) was secured after a slight change in method. The reaction mixture was not stirred for twenty-four hours at room temperature, and the ketone was removed and purified after a reaction time of only three hours. This method was tried with both 1-(4-methoxyphenoxy)-2-propanone (I) and 1-(4-propoxyphenoxy)-2-propanone (III), and in both cases a twenty per cent increase in yield was secured.

The lowest yield (48%) was obtained in the preparation of 1-(2-methoxy-4-methylphenoxy)-2-propanone (V). This low yield was probably due to interference of the methoxy group in the 2-position.

The aryloxyketones were condensed with isatin, 5-methylisatin, and 5-chloroisatin to form substituted 4-quinaldinecarboxylic acids.

The time required for condensation decreased when a 5-substituted isatin was used. The average time required for condensation with isatin was six hours, with 5-methylisatin four hours, and with 5-chloroisatin thirty minutes.

Most of the yields were between sixty and seventy per cent of theoretical. The lower yields were thought to have been caused by a slight increase in solubility of the quinoline acid in water. It was noted that if a chloro group was added in the 6-position the solubility increased, and if a methyl group was added in the 6-position the solubility decreased.

For example, 6-chloro-3-(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (XIX) is more soluble than 3-(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (IX).

The potassium salts of the compounds prepared possessed soap-like properties and showed a tendency to foam in water solution. The potassium salts of all the compounds prepared except those of 3-(2-methoxy-4-methylphenoxy)-4-quinaldinecarboxylic acid (XIII) were salted out by the high concentration of potassium hydroxide.

The quinoline acids darkened at about 165 degrees and decarboxylation was observed to start well below the melting point which varied with the rate of heating. Thus values listed as melting points (decomposition) have little significance as a characteristic of the compound. The decomposition-point temperature in all cases decreased as the length of the alkoxy chain increased. Thus the 3-(4-butoxyphenoxy)-4-quinaldinecarboxylic acids had the lowest melting point.

The semi-micro method of Dumas was used for the nitrogen determinations. The 6-chloro-quinoline acids burned rapidly in the combustion train, and it was necessary to employ a very low flame at the start of the run with a gradual increase in temperature until the end of the analysis.

A rapid combustion at high temperature always resulted in a high nitrogen percentage for the chloro acids, probably because of the formation of methane.

CHAPTER V

SUMMARY

SUMMARY

The following compounds have been prepared, and a study made of some of their properties:

1. Ketones

   1-(4-methoxyphenoxy)-2-propanone (I)

   1-(4-ethoxyphenoxy)-2-propanone (II)

   1-(4-propoxyphenoxy)-2-propanone (III)

   1-(4-butoxyphenoxy)-2-propanone (IV)

   1-(2-methoxy-4-methylphenoxy)-2-propanone (V)

2. Ketone Derivatives

   The 2,4-dinitrophenylhydrazone and the semicarbazones of:

   1-(4-methoxyphenoxy)-2-propanone (I)

   1-(4-ethoxyphenoxy)-2-propanone (II)

   1-(4-propoxyphenoxy)-2-propanone (III)

   1-(4-butoxyphenoxy)-2-propanone (IV)

   1-(2-methoxy-4-methylphenoxy)-2-propanone (V)

3. Substituted Quinoline Acids

   3-(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (IX)

   3-(4-ethoxyphenoxy)-4-quinaldinecarboxylic acid (X)

   3-(4-propoxyphenoxy)-4-quinaldinecarboxylic acid (XI)

   3-(4-butoxyphenoxy)-4-quinaldinecarboxylic acid (XII)

   3-(2-methoxy-4-methylphenoxy)-4-quinaldinecarboxylic acid (XIII)

   6-methyl-3-(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (XIV)

   6-methyl-3-(4-ethoxyphenoxy)-4-quinaldinecarboxylic acid (XV)

   6-methyl-3-(4-propoxyphenoxy)-4-quinaldinecarboxylic acid (XVI)

   6-methyl-3-(4-butoxyphenoxy)-4-quinaldinecarboxylic acid (XVII)

6-methyl-3-(2-methoxy-4-methylphenoxy)-4-quinaldinecarboxylic acid (XVIII)

6-chloro-3-(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (XIX)

6-chloro-3-(4-ethoxyphenoxy)-4-quinaldinecarboxylic acid (XX)

6-chloro-3-(4-propoxyphenoxy)-4-quinaldinecarboxylic acid (XXI)

6-chloro-3-(4-butoxyphenoxy)-4-quinaldinecarboxylic acid (XXII)

6-chloro-3-(2-methoxy-4-methylphenoxy)-4-quinaldinecarboxylic acid (XXIII)

APPENDIX I

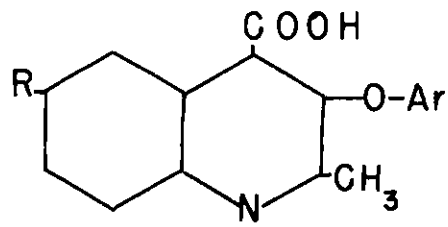
TABLE I

Alkoxyaryloxyacetones and Derivatives

ArO in $ArOCH_2COCH_3$	Yield %	M.p. Degrees C.	2,4-Dinitrophenylhydrazone	Semicarbazone
4-Methoxyphenoxy	64	48.5	149	192.5
4-Ethoxyphenoxy	62	35.5	105.5	192
4-Propoxyphenoxy	73	39	91.5	188.8
4-Butoxyphenoxy	69	37	153	187.8
2-Methoxy-4-methylphenoxy	48	28.5	136	153

TABLE II

3-Alkoxyaryloxy-4-quinaldinecarboxylic Acids



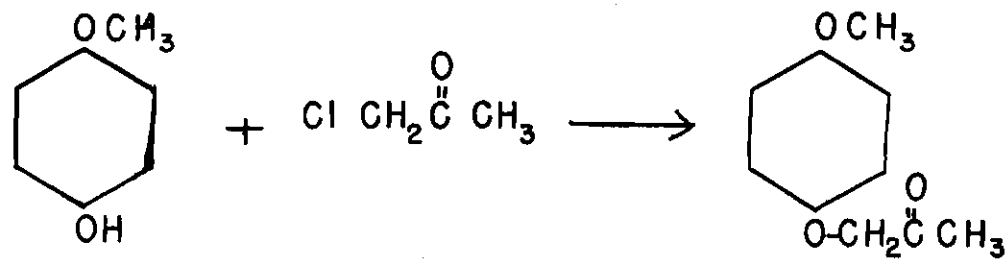
R	Ar	Yield %	M.p. degrees C. (dec)	Nitrogen % Calcd.	Found
H	4-Methoxy-phenyl	74	215	4.56	4.20
H	4-Ethoxy-phenyl	56	214	4.33	4.19
H	4-Propoxy-phenyl	70	208	4.15	4.14
H	4-Butoxy-phenyl	77	150	3.99	3.70
H	2-Methoxy-4-Methyl-phenyl	75	232	4.33	4.14
CH_3	4-Methoxy-phenyl	67	234	4.33	4.25
CH_3	4-Ethoxy-phenyl	64	198	4.15	4.30
CH_3	4-Propoxy-phenyl	62	204	3.99	4.01
CH_3	4-Butoxy-phenyl	60	193	3.83	3.85

R	Ar	Yield %	M.p. degrees C. (dec)	Nitrogen % Calcd.	Found
CH_3	2-Methoxy-4-Methyl-phenyl	54	242	4.15	4.19
Cl	4-Methoxy-phenyl	40	237	4.08	4.00
Cl	4-Ethoxy-phenyl	82	222	3.91	3.66
Cl	4-Propoxy-phenyl	68	205	3.77	3.48
Cl	4-Butoxy-phenyl	67	163	3.63	3.70
Cl	2-Methoxy-4-Methyl-phenyl	42	215	3.73	3.91

APPENDIX II

FIGURE 1

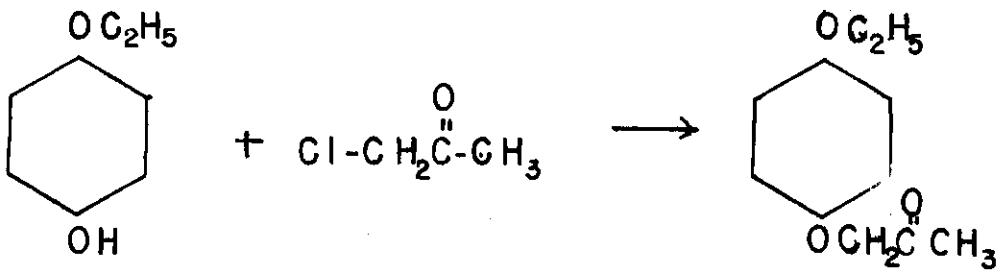
Preparation of 1-(4-Methoxyphenoxy)-2-propanone (I)



(I)

FIGURE 2

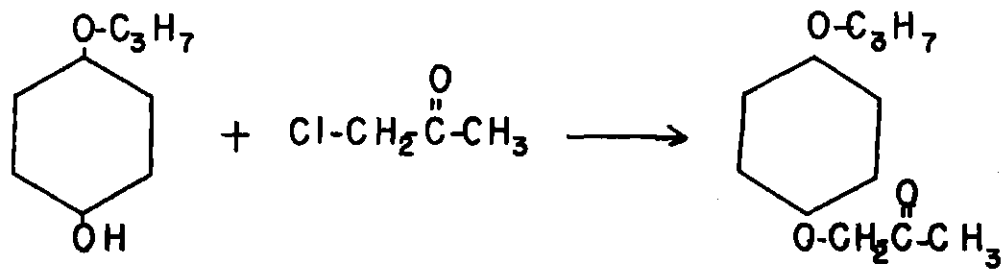
Preparation of 1-(4-Ethoxyphenoxy)-2-propanone (II)



(II)

FIGURE 3

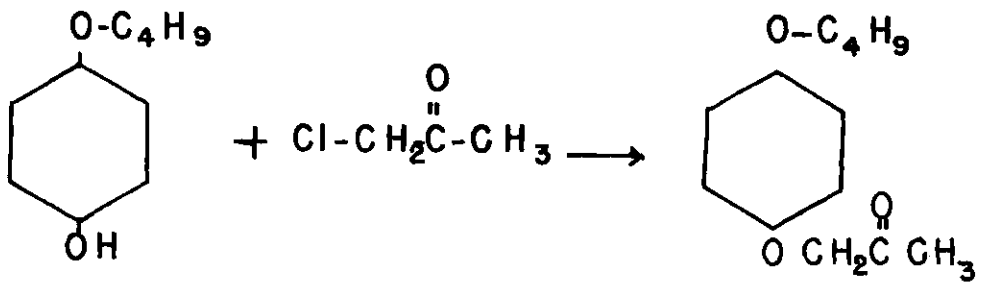
Preparation of 1-(4- Propoxyphenoxy)– 2-propanone (III)



(III)

FIGURE 4

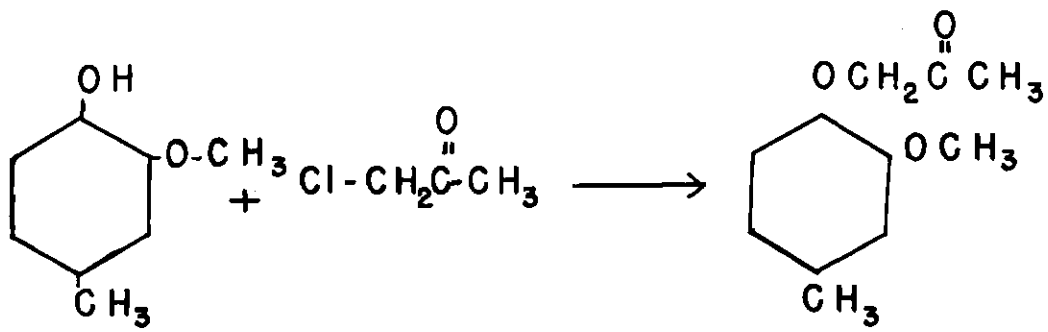
Preparation of 1-(4–Butoxyphenoxy) - 2-propanone (IV)



(IV)

FIGURE 5

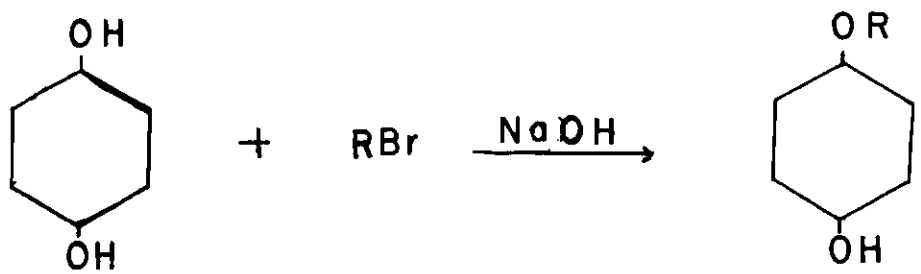
Preparation of 1-(2-Methoxy-4-methylphenoxy)-2-propanone (V)



(V)

FIGURE 6

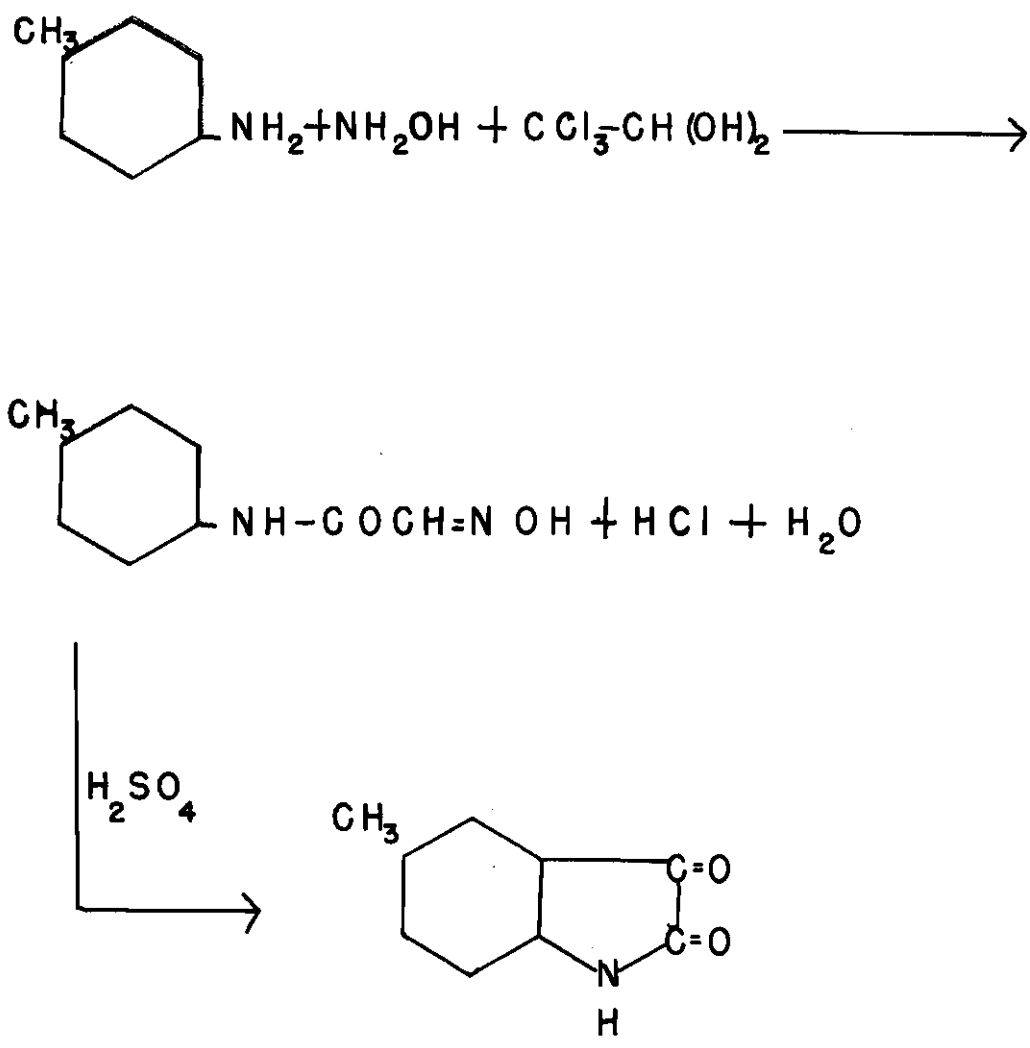
Preparation of Alkoxyphenol (VI)



(VI)

FIGURE 7

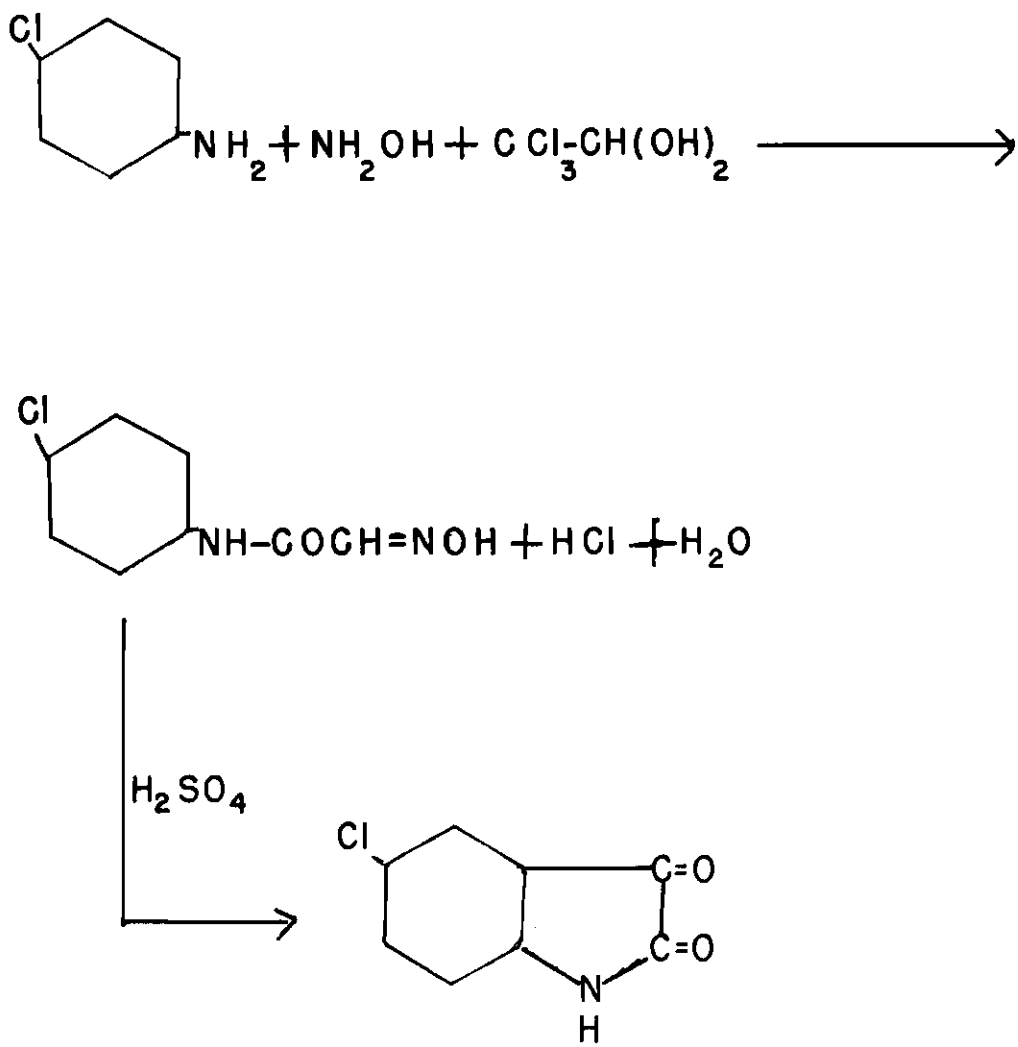
Preparation of 5-Methylisatin(VII)



(VII)

FIGURE 8

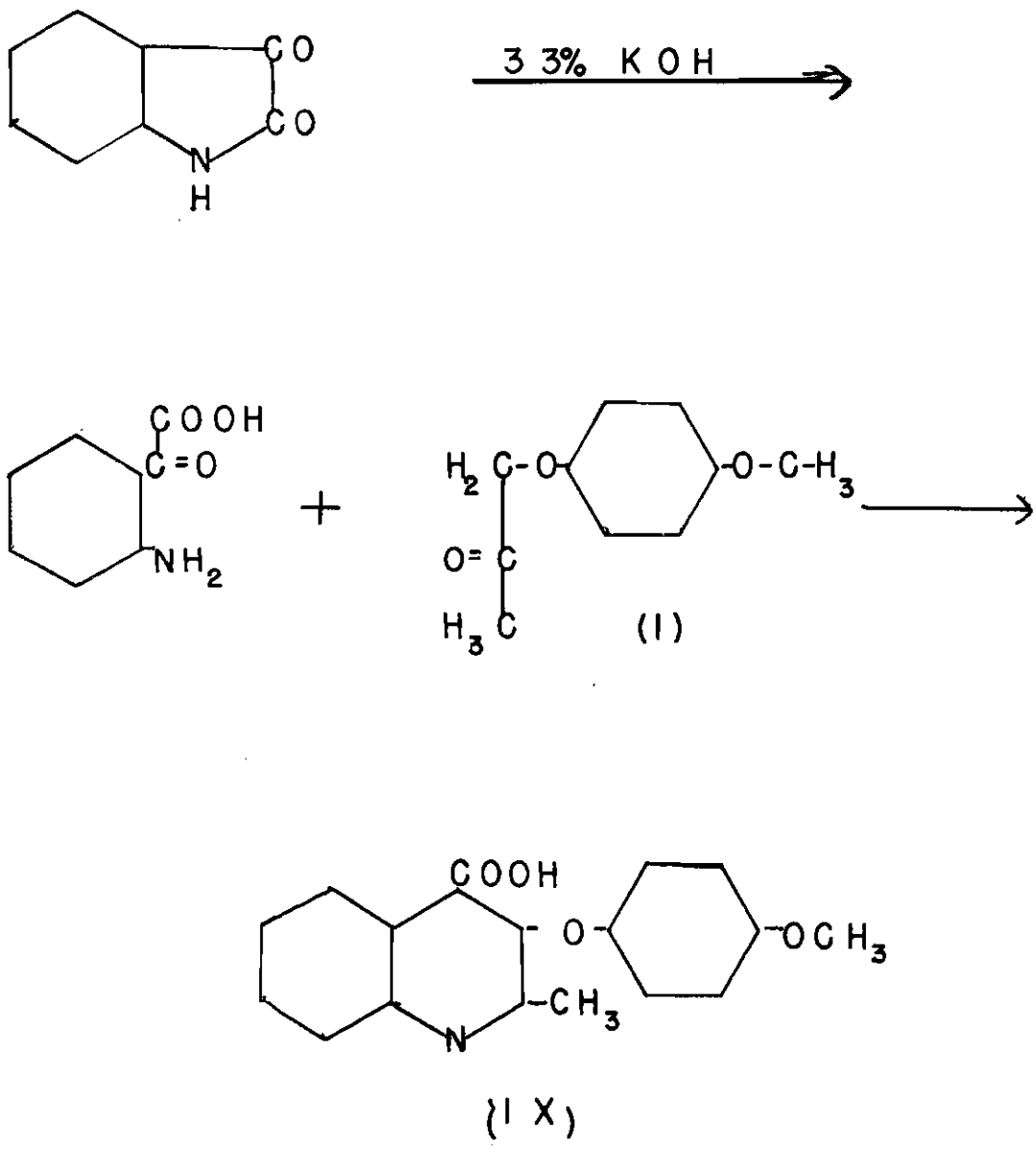
Preparation of 5-Chloroisatin (VIII)



(VIII)

FIGURE 9

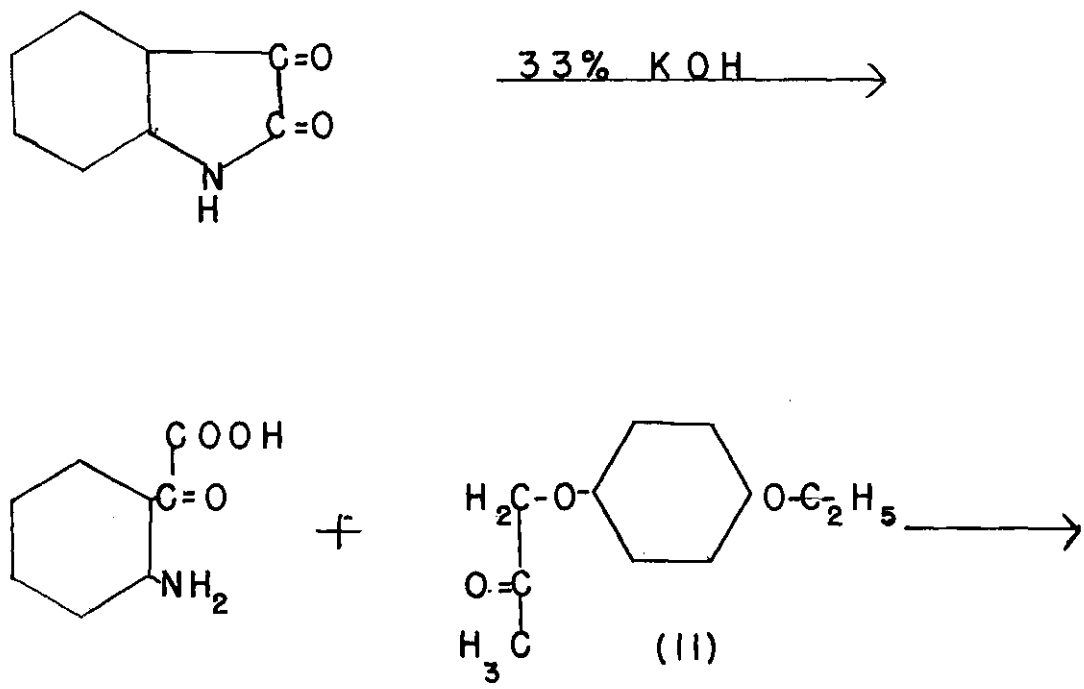
Preparation of 3-(4-Methoxyphenoxy)-4-quinaldinecarboxylic acid (IX)



(IX)

FIGURE 10

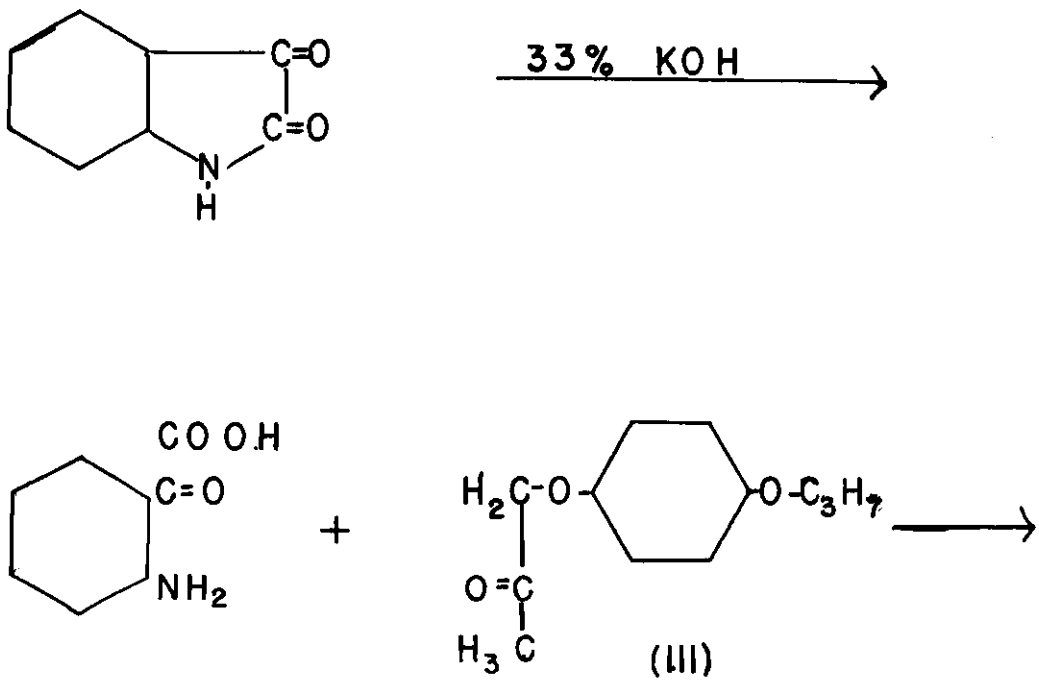
Preparation of 3-(4- Ethoxyphenoxy)-4-quinaldinecarboxylic acid (X)

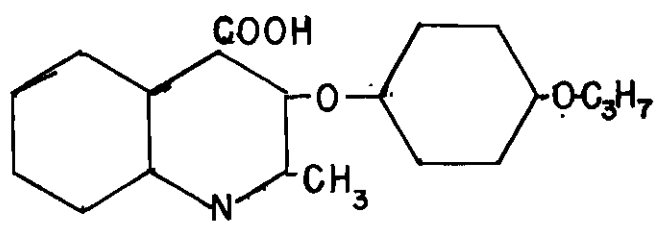


(X)

FIGURE II

Preparation of 3-(4-Propoxyphenoxy)-4-quinaldinecarboxylic acid (XI)

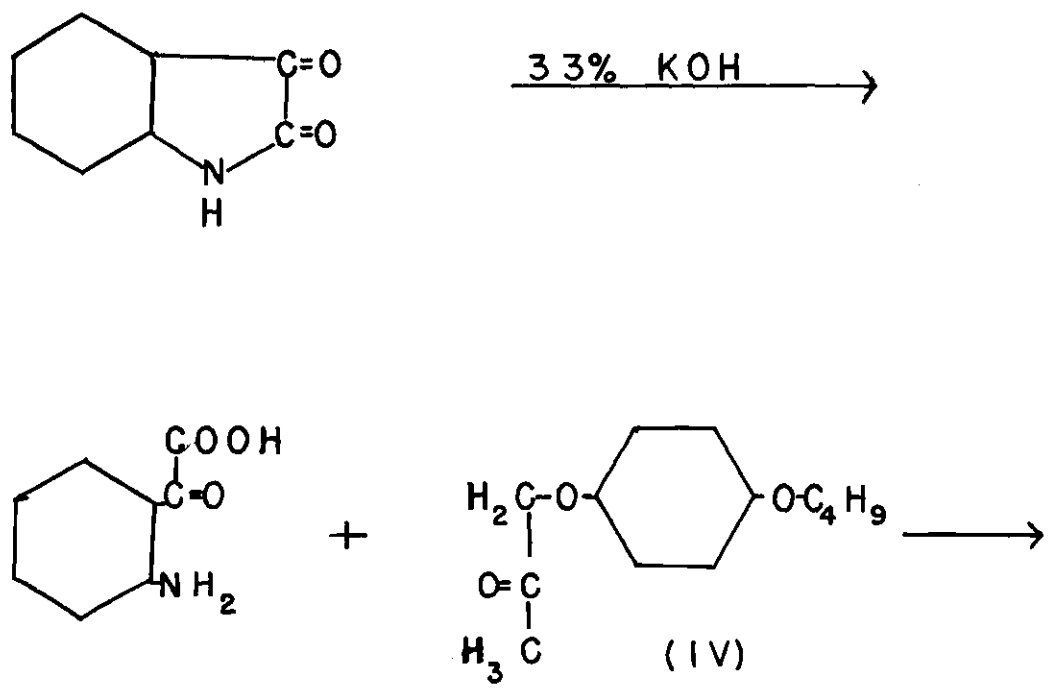




(XI)

FIGURE 12

Preparation of 3-(4-Butoxyphenoxy)-4-quinaldinecarboxylic acid (XII)



(XII)

FIGURE 13

Preparation of 3-(2-Methoxy-4-methylphenoxy)-4-quinaldinecarboxylic acid (XIII)

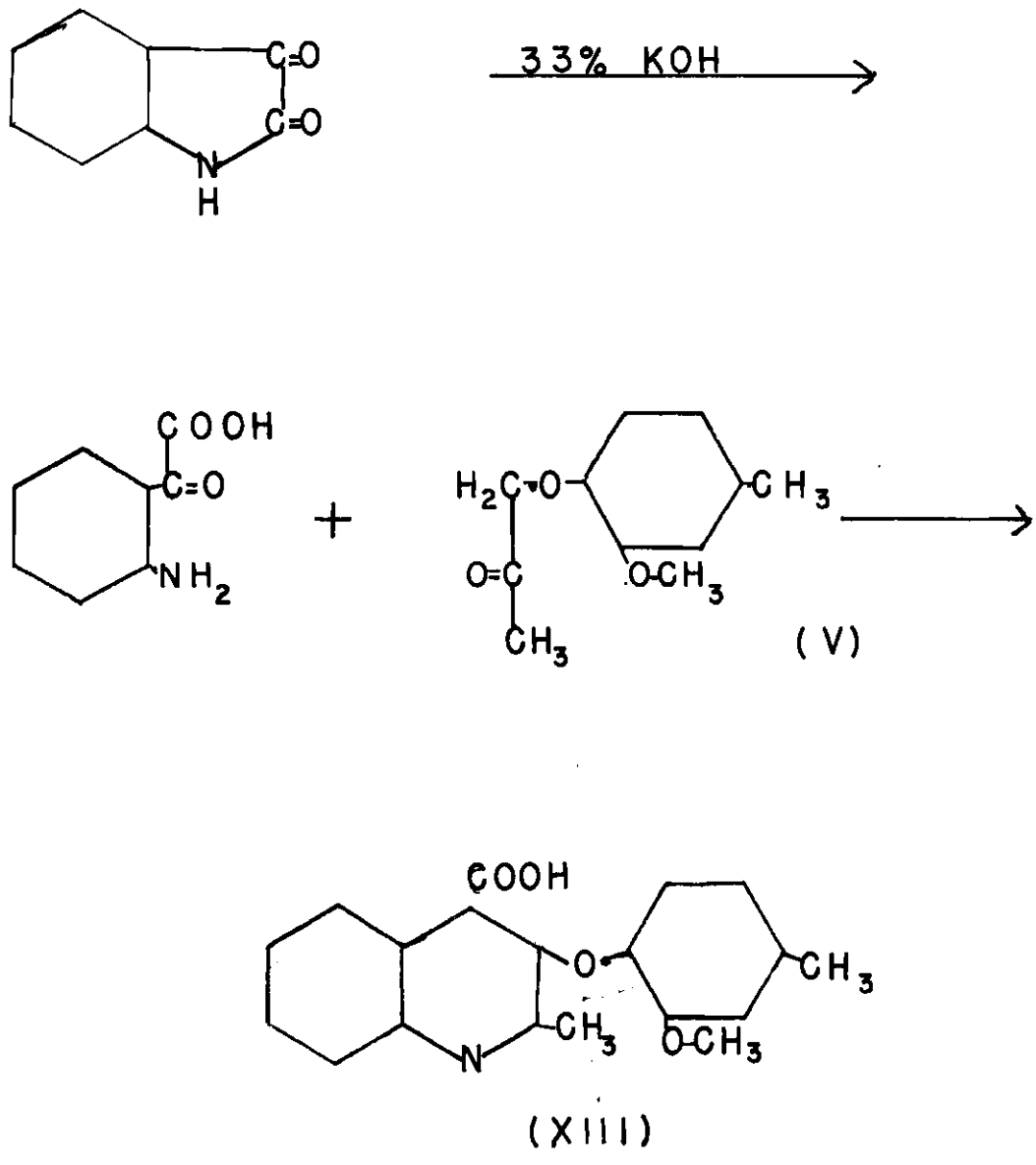


FIGURE 14

Preparation of 6-Methyl-3(4-methoxyphenoxy)-4-quinaldinecarboxylic acid (XIV)

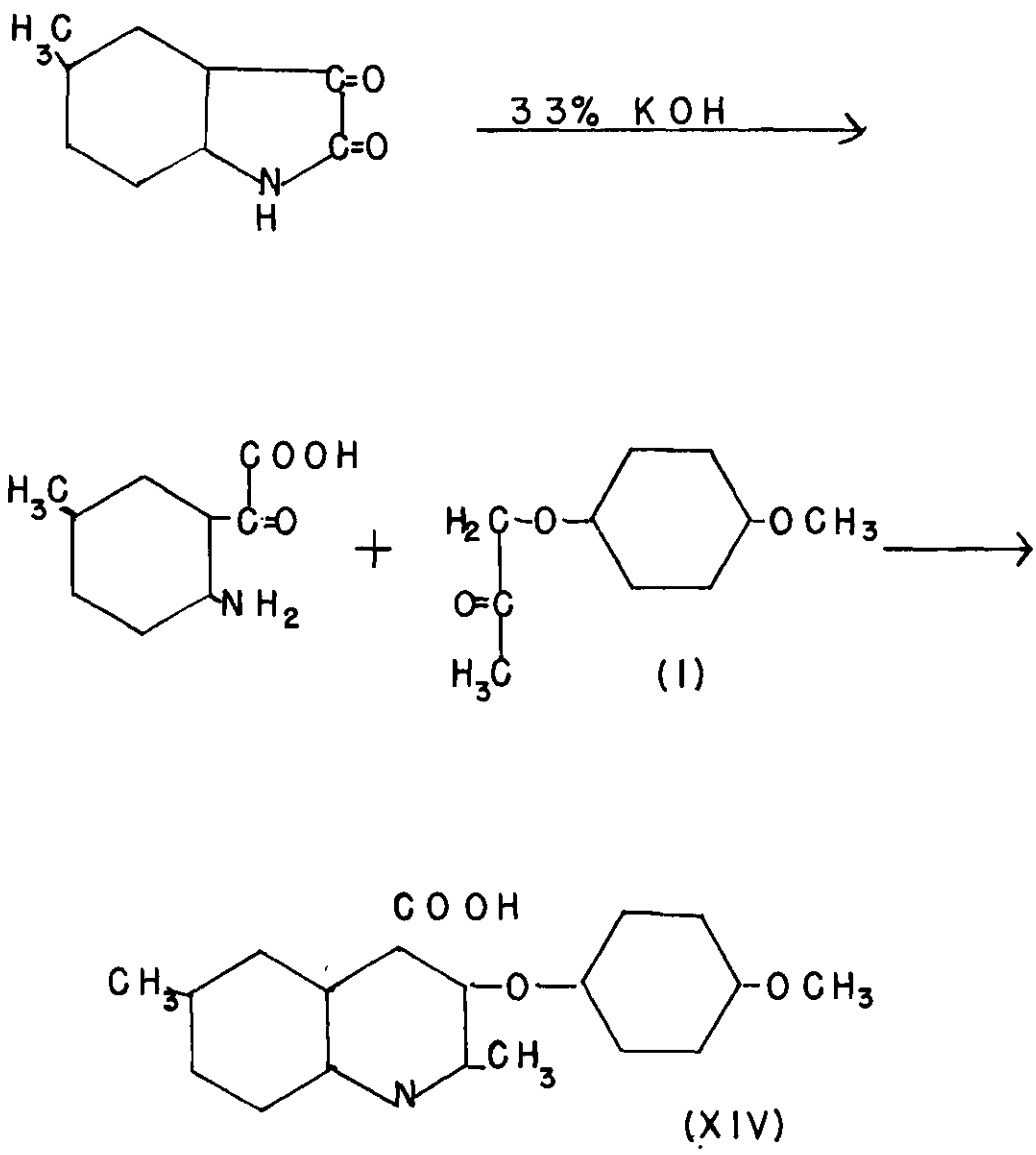


FIGURE 15

Preparation of 6-Methyl-3(4-ethoxyphenoxy)-4-quinaldinecarboxylic acid (XV)

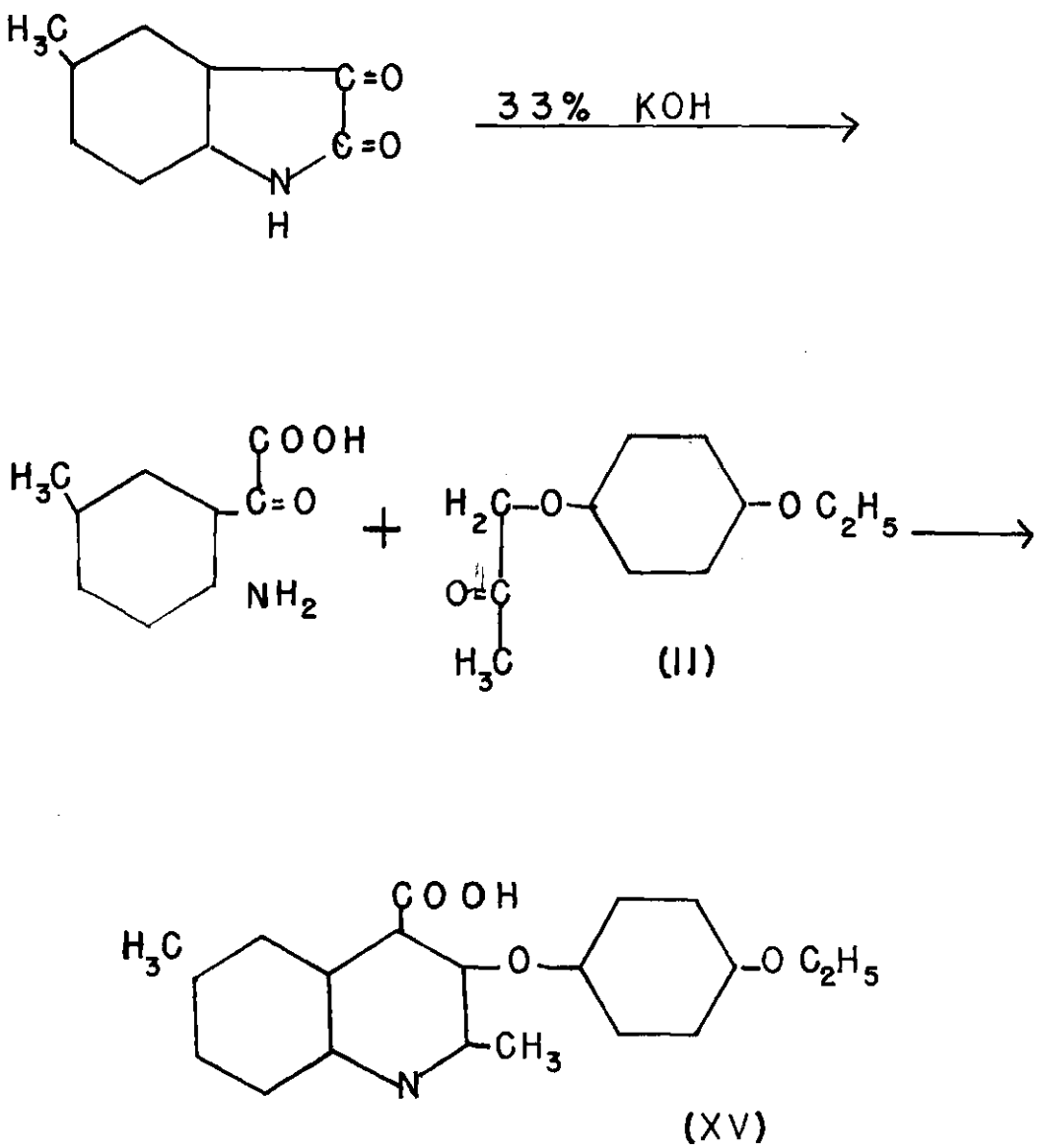


FIGURE 16

Preparation of 6-Methyl-3-(4-propoxyphenoxy)-4-quinaldinecarboxylic acid (XVI)

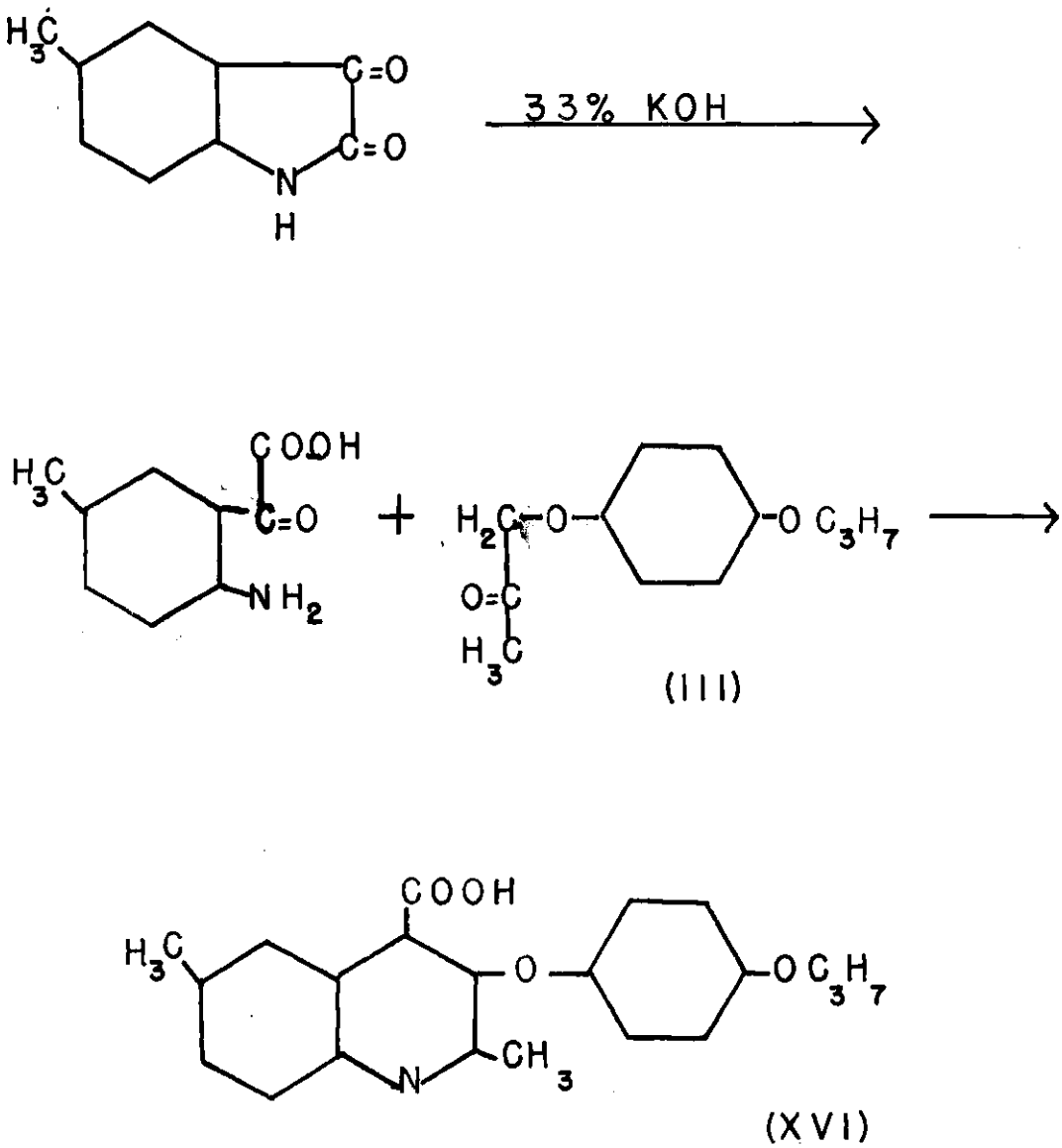


FIGURE 17

Preparation of 6-Methyl-3-(4-butoxyphenoxy)-4-quinaldinecarboxylic acid (XVII)

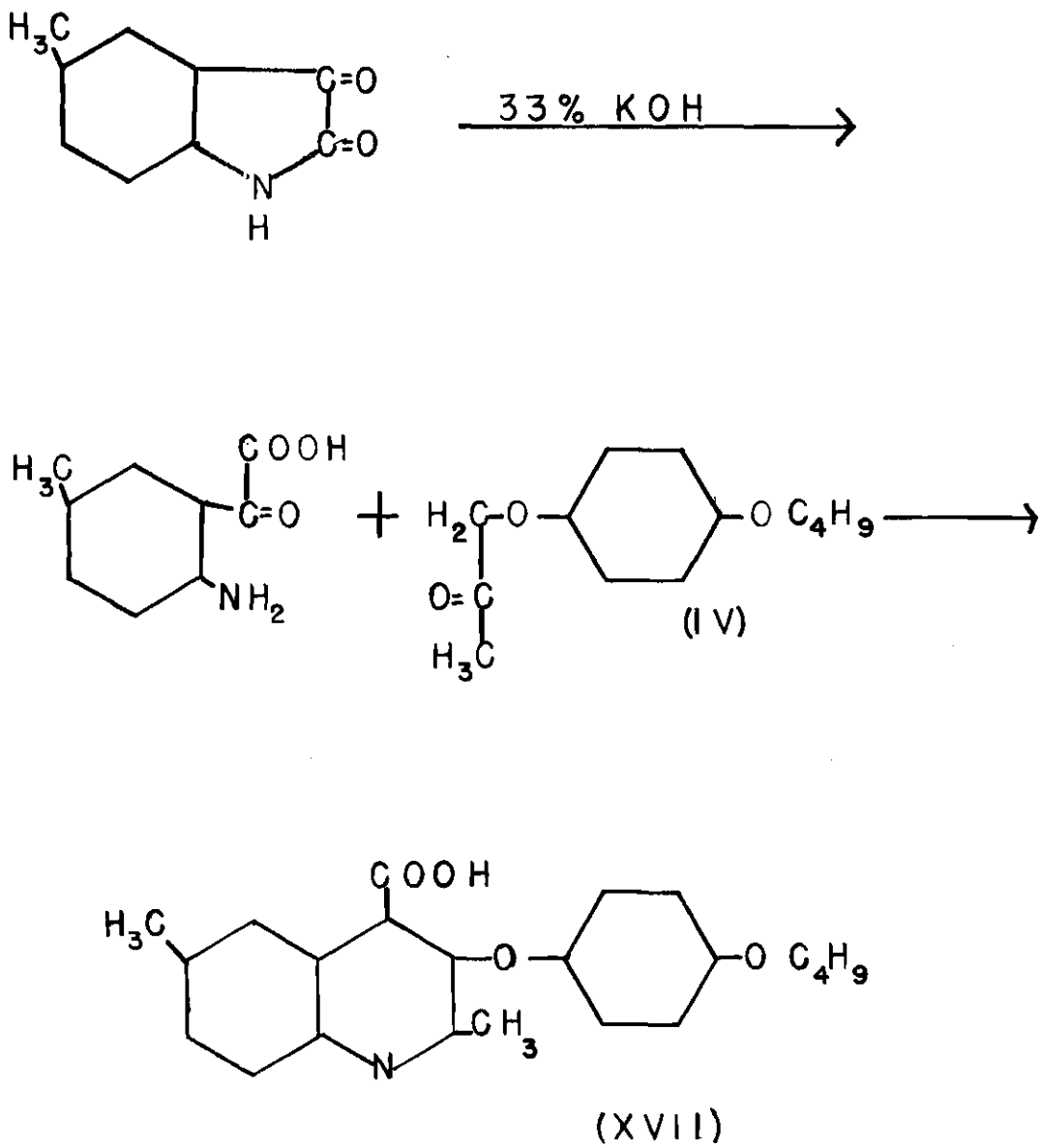


FIGURE 18

Preparation of 6-Methyl-3(2-methoxy-4-methyl-phenoxy-4-quinaldinecarboxylic acid (XVIII)

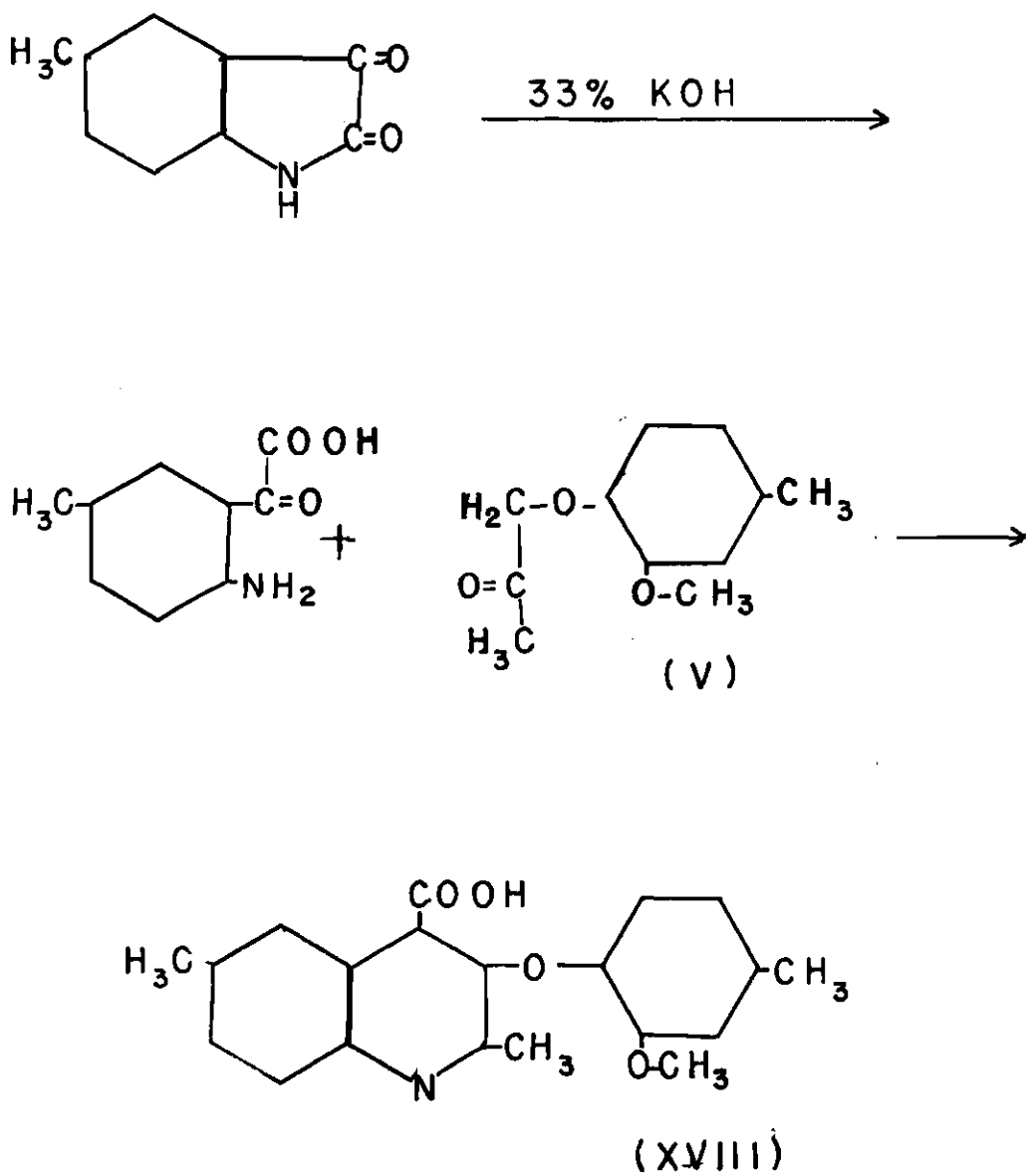


FIGURE 19

Preparation of 6-Chloro-3-(4-methoxyphenoxy-4-quinaldinecarboxylic acid (XIX)

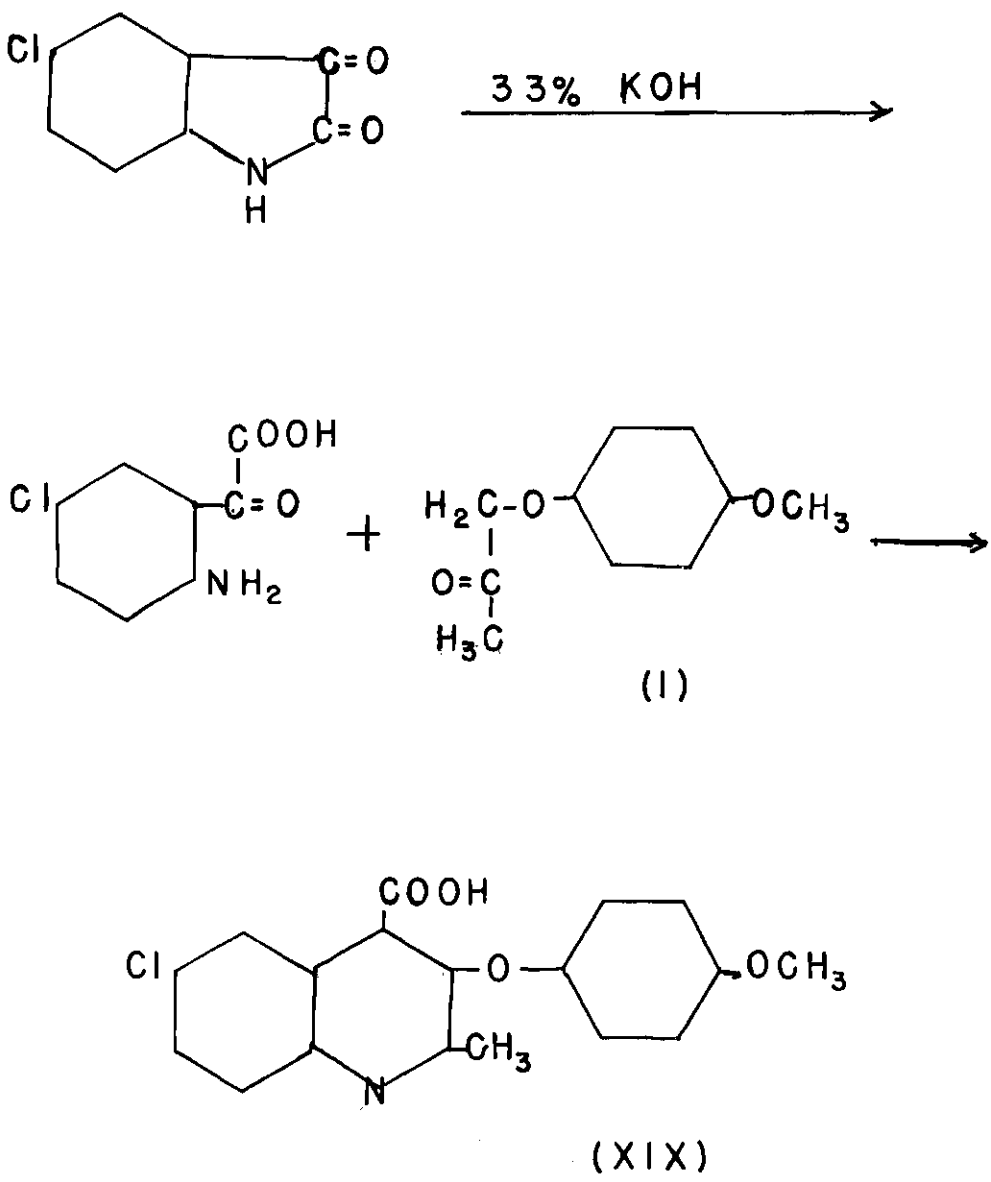


FIGURE 20

Preparation of 6-Chloro-3-(4-ethoxyphenoxy-4-quinaldinecarboxylic acid (XX)

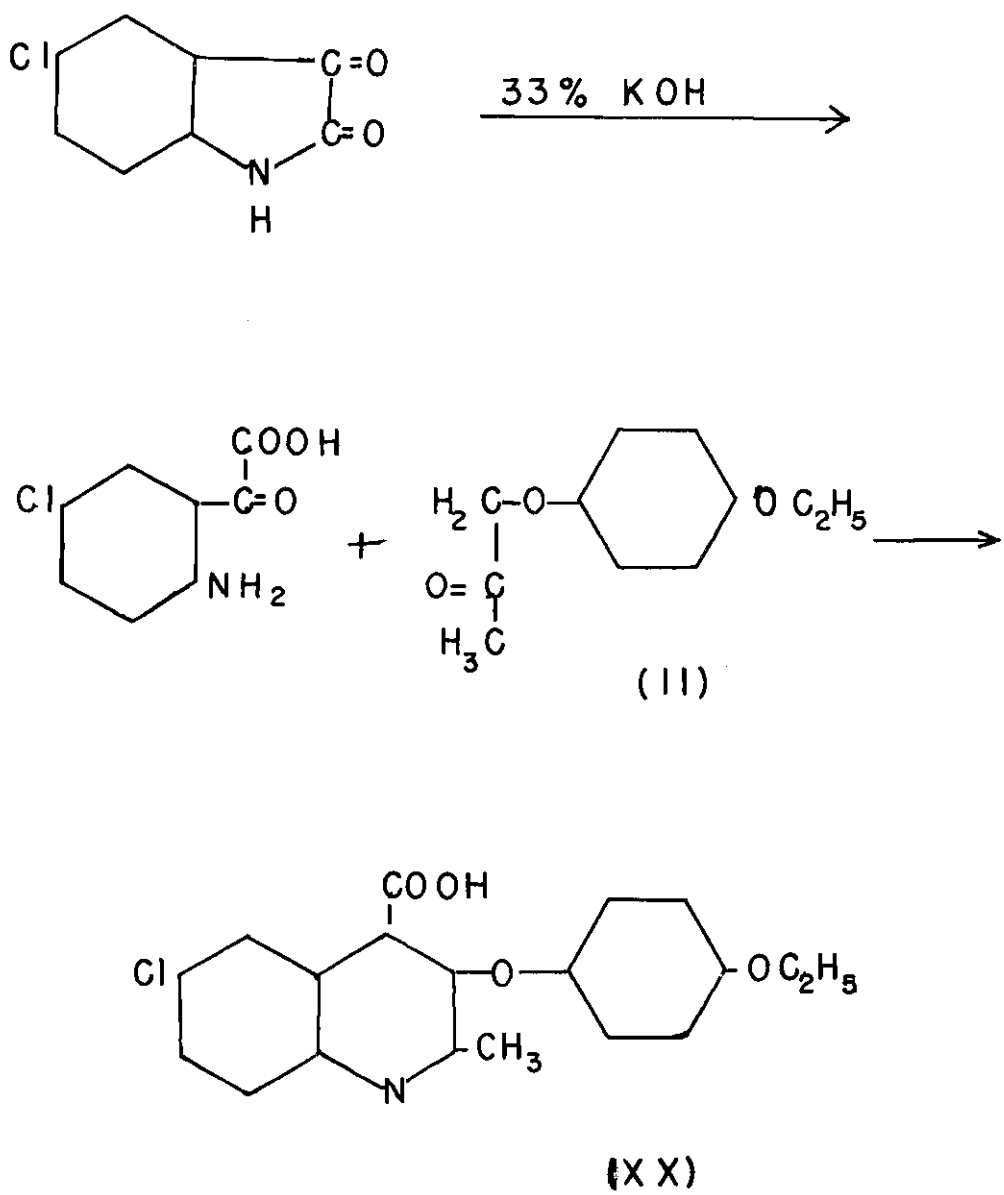


FIGURE 21

Preparation of 6-Chloro-3(4-propoxyphenoxy)-4-quinaldinecarboxylic acid (XXI)

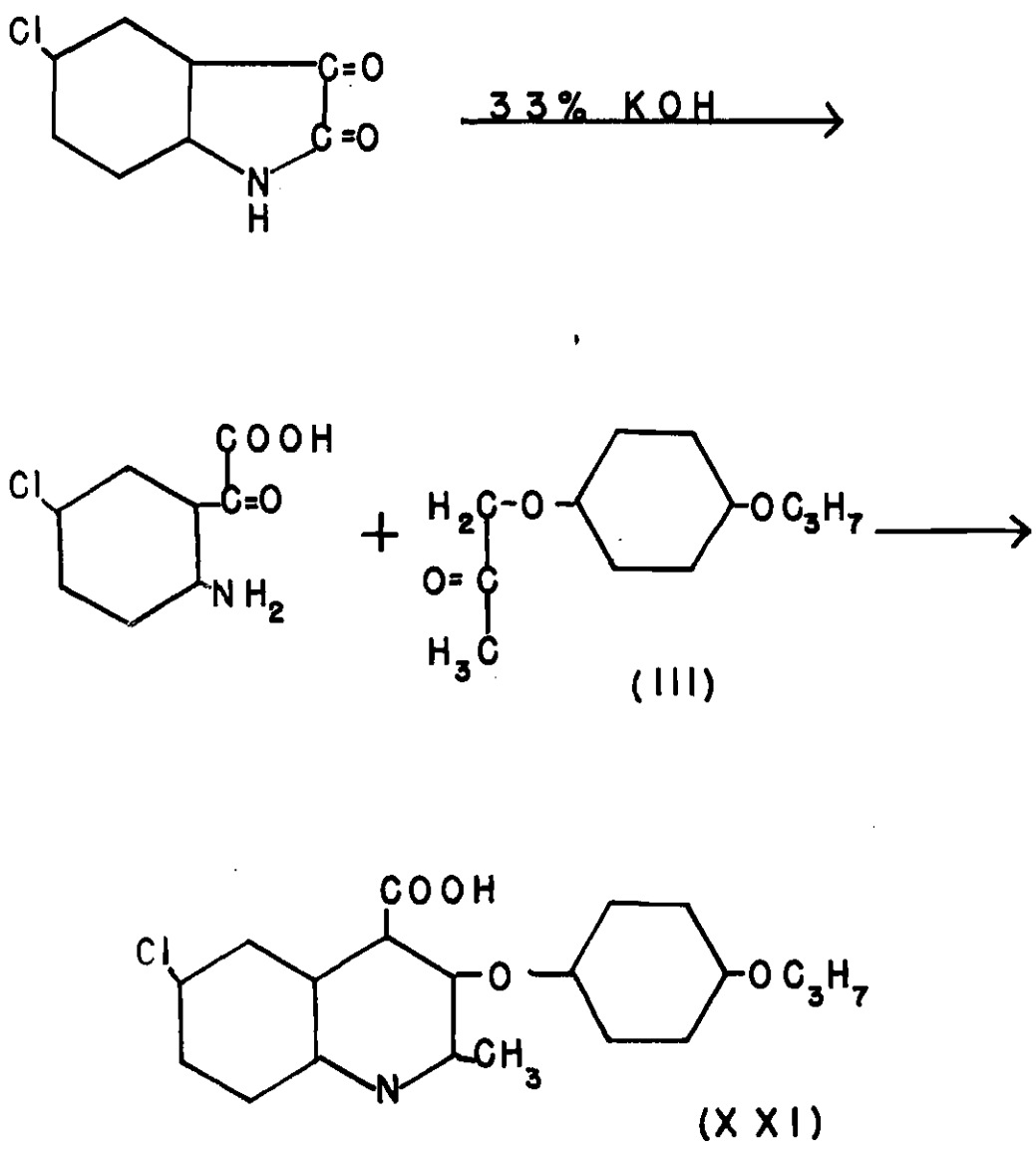


FIGURE 22

Preparation of 6-Chloro-3(4-butoxyphenoxy)-4-quinaldinecarboxylic acid (XXII)

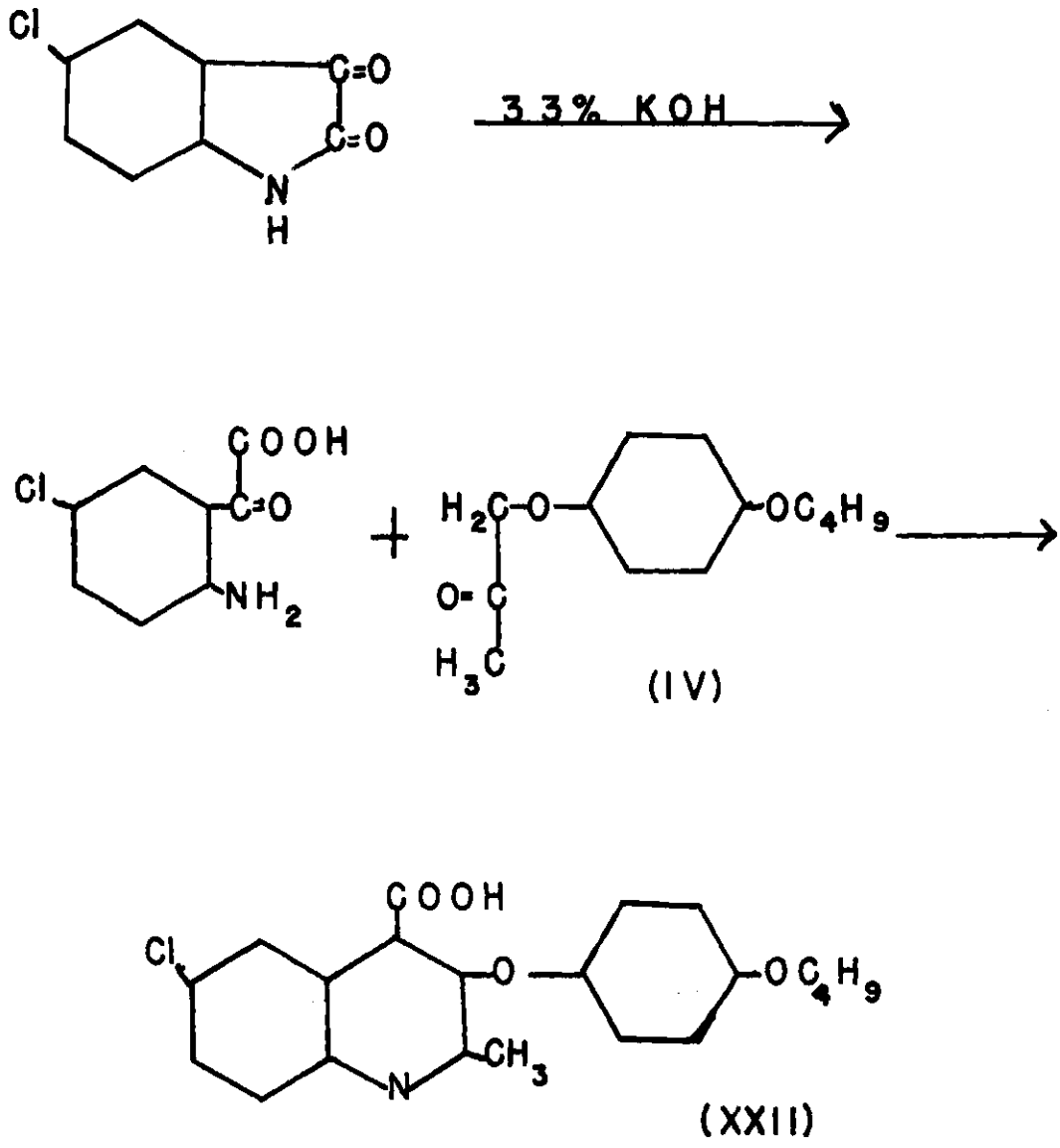
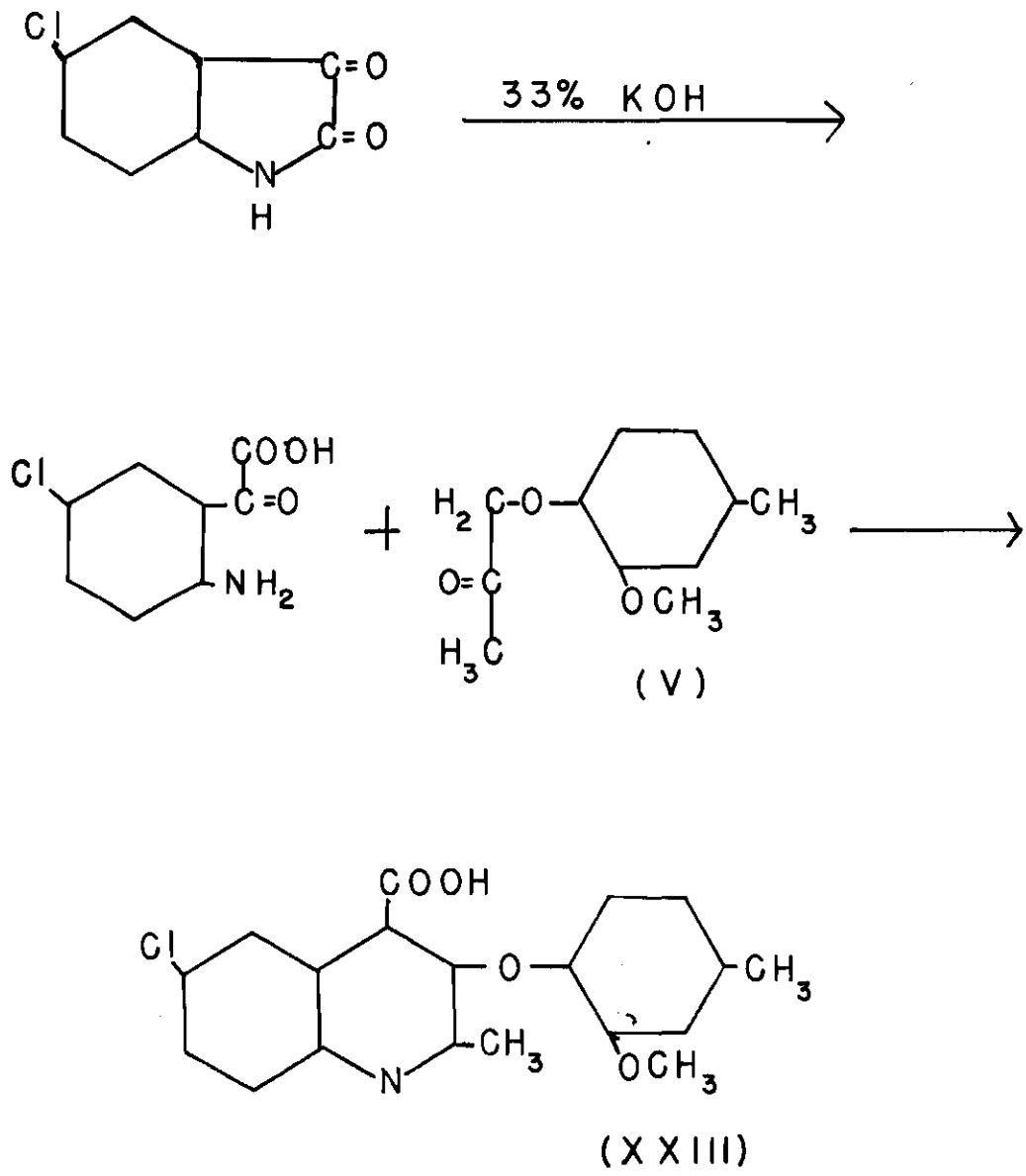


FIGURE 23

Preparation of 6-Chloro-3-(2-methoxy-4-methylphenoxy)-4-quinaldinecarboxylic acid (XXIII)



BIBLIOGRAPHY

BIBLIOGRAPHY

Calaway and Henze, Journal of the American Chemical Society, 61: 1355 (1939)

Dowell, Georgia School of Technology, Master's Thesis (1947)

Gatterman, The Practical Methods of Organic Chemistry, third English edition, Macmillan Company (1925)

Gilman, Organic Synthesis, John Wiley and Sons, Inc., vol. I, p. 321 (1932)

Hurd and Perletz, Journal of the American Chemical Society, 68: 38 (1946)

Knight, Georgia School of Technology, Master's Thesis (1944)

Knight, Porter, and Calaway, Journal of the American Chemical Society, 66: 1893 (1944)

Morton, Chemistry of Heterocyclic Compounds, McGraw-Hill Book Company, p. 262 (1946)

Newell and Calaway, Journal of the American Chemical Society, 69: 116 (1947)

Pfitzinger, Journal fur praktische Chemie, 33: 100 (1896)

_____, Journal fur praktische Chemie, 38: 584 (1888)

_____, Journal fur praktische Chemie, 56: 283 (1897)

Von Braum, Gmelin, and Schulthesis, Berichte der deutschen chemischen Gesellschaft, 56: 1344 (1923)